OXYTOCIN USE IN OBSTETRIC PRACTICE AND ITS ASSOCIATION WITH POSTPARTUM HEMORRHAGE AND PRIMARY CESAREAN SECTION IN THE UNITED STATES

by

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ABSTRACT

Background: Oxytocin is a life-saving, high-alert medication.[1] While frequently used in obstetric practice to induce or augment labor as well as prevent or treat postpartum hemorrhage, little is known about the levels and patterns of oxytocin use in obstetric practice in the United States. The purpose of this dissertation is to describe how oxytocin is being used in intrapartum care in the US and what are the patters of association with postpartum hemorrhage and primary cesarean section.

Methods: This study is a secondary data analysis of the Consortium on Safe Labor Database from the National Institute of Health. The analytic sample consisted of data from women admitted for delivery at 9 of 12 study sites that collected any oxytocin data; women were excluded from analysis if admitted for a pre-labor cesarean section. Descriptive statistics were used to describe oxytocin exposure patterns. Associations between oxytocin exposure and postpartum hemorrhage and primary cesarean section were assessed using multivariable logistic regression. The regression models were then used to predict probabilities.

Results: **162,201 births were included in the analysis. Of these, oxytocin dose information had been collected for 54,456 births.** 65.7% of women in the sample were exposed to oxytocin during their labor. 2.9% and 14% of women had a PPH diagnosis and primary cesarean, respectively. 66% of births in the sample involved oxytocin exposure during labor. The probability of postpartum hemorrhage was significantly increased at 6,000 mU of total oxytocin dose exposure, while the probability of primary cesarean section was significantly increased at 4,400 mU of total oxytocin dose exposure. Maximum oxytocin infusion rates greater than 10 mU/min and 20 mU/min were associated with increased risks of primary cesarean and postpartum hemorrhage, respectively.

Conclusion: The results suggest that oxytocin may be used frequently and has a dose-dependent association with two important obstetric outcomes: postpartum hemorrhage and primary cesarean section. Prospective studies are needed to corroborate this study's findings and to examine whether oxytocin is being used inappropriately as a way to develop clinical guidance and interventions on its adequate use in obstetric practice.

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INTRODUCTION AND BACKGROUND

Introduction

Oxytocin is the hormone associated with orgasm, labor contractions, milk let-down and social bonding.[2] Oxytocin in its synthetic form is commonly used in obstetric practice to induce or augment labor, as well as prevent or treat postpartum hemorrhage (PPH).

PPH is a leading cause of maternal morbidity and mortality.[3] While maternal mortality rates have decreased globally, rates of atonic PPH, the most common type of PPH, have increased in a number of high-resource countries (e.g., Australia, Canada, Ireland, US, UK).[4–11] Morbidity related to PPH is significant and may include outcomes ranging from anemia and difficulty breastfeeding to loss of fertility, postpartum depression and post-traumatic stress disorder.[12,13] Observational studies in the United States have found that patient risk factors for PPH explain little of the rise in atonic PPH.[4,5,8,10,11] Most of these studies have used the National Inpatient Sample, which provides demographic data and International Classification of Disease (ICD) codes; the ICD, however, does not contain all codes pertinent to PPH and associated risks.[5,8,10,11] Specifically, the ICD does not contain codes for labor augmentation and, especially, for either induction or augmentation performed with synthetic oxytocin. Exposure to synthetic oxytocin in labor is an established risk factor for atonic PPH[14–16] and the extent of synthetic oxytocin use in obstetric practice may be increasing.[17,18] Oxytocin use is also associated with another significant maternal outcome and focus of national quality initiatives, the primary cesarean section.[19–22]

Currently, 32% of births in the United States are cesarean sections.[23] Cesarean sections are major abdominal surgeries associated with a number of adverse outcomes, including an increased risk for hemorrhage, infection, neonatal respiratory distress and complications with

future pregnancies.[24,25] Reducing primary cesareans in low-risk women is a quality indicator for the Center for Medicare and Medicaid Services' Obstetric Core Measures, as well as a Healthy People 2020 goal and an initiative for the American College of Nurse-Midwives and the American Congress of Obstetricians and Gynecologists[25–28]. Oxytocin use is an independent risk factor for cesarean sections.[19–22,29]

Background

Induction or augmentation of labor is an independent risk factor for PPH.[8,30–32] Oxytocin is the drug commonly used for both induction and augmentation, and its use in labor may explain much of the increase in atonic PPH in high-resource countries.[15] Similarly, labor induction is an independent risk factor for primary cesareans, with oxytocin being the medication commonly used for induction.[19–22] Induction and augmentation rates in obstetric practice in the United States are high, but both terms cover a wide array of procedures (e.g., mechanical induction with cervical dilators to augmentation with artificial rupture of membranes to the use of oxytocin).[33–35] The incidence and pattern of oxytocin exposure in laboring women in hospitals in the United States is unknown. Oxytocin is a high-risk medication[1] and it is possible that its use is the main reason why induction and augmentation are independent risk factors for PPH and primary cesareans. In order to address the high rates of PPH and primary cesareans, improve the quality of obstetric care, maternal and neonatal outcomes, oxytocin use must be better understood.

Purpose of Dissertation Research

The purpose of this study is to examine the use of synthetic oxytocin in obstetric practice and its patterns of association with postpartum hemorrhage and primary cesarean section by using a nationwide sample of hospitals with inpatient obstetric units.

Specific Aims/Hypotheses

Aim 1

Aim 1a: To examine the incidence of synthetic oxytocin exposure in women admitted for labor in a large nationwide sample of hospitals.

Aim 1b: Among women who received synthetic oxytocin, to describe synthetic oxytocin exposure via "total dose", stratified by indication and patient characteristics.

Hypothesis: The majority (i.e., > 50%) of hospital labors observed will include synthetic oxytocin exposure. The primary use of synthetic oxytocin will be for labor augmentation.

Aim 2

Aim 2a: To examine the relationship between synthetic oxytocin exposure and postpartum hemorrhage accounting for patient-, provider- and hospital-level variables.

Aim 2b: For those that received synthetic oxytocin, examine the relationship between amount received as measured by "total dose" and postpartum hemorrhage accounting for patient-, provider- and hospital-level variables.

Aim 2b Sub-Aim: Explore whether there is a clinically-relevant point of oxytocin exposure associated with the risk of PPH.

Hypothesis: Increased dose of synthetic oxytocin will be associated with higher risk of PPH among women treated independent of patient characteristics.

Aim 3

Aim 3a: To examine the relationship between the receipt of synthetic oxytocin and unscheduled cesarean accounting for patient-, provider- and hospital level variables.

Aim 3b: For those that received synthetic oxytocin, examine the relationship between amount received as measured by "total dose" and unscheduled cesarean accounting for patient-, provider and hospital-level variables.

Aim 3b Sub-Aim: Explore whether there is a clinically-relevant point of oxytocin exposure associated with the risk of a primary, unscheduled cesarean section.

Hypothesis: Oxytocin exposure will be positively associated with the occurrence of primary, unscheduled cesarean sections independent of patient-level variables.

Significance of Research

The significance of the proposed research lies in its focus and method. Oxytocin may be the most commonly used drug (apart from pain medications) in U.S. obstetric practice, but little research has been done on exactly how and to what extent oxytocin is used. Since oxytocin exposure is an independent risk factor for both PPH and primary cesareans, understanding how it is used is critical for developing interventions to address significant causes of maternal morbidity and to improve quality care and outcome measures. Oxytocin exposure is difficult to measure and the proposed research will use total dose, a newer measure[36,37] and one that holds promise for understanding clinically relevant points of oxytocin exposure. The use of total dose in this research will not only allow a more nuanced understanding of oxytocin's effect on important outcomes but will also contribute to the science regarding the use of this method for future research. This study also uses regression models to predict probabilities, allowing for easier interpretation that more accurately depicts risk, especially when the outcome of interest, such as cesarean section, is common.

Conceptual Framework

Joanne Duffy's Quality-Caring Model[38] (QCM) provides the conceptual framework for this research. The QCM combines "theories of health care quality and relational aspects of nursing"[38(p30)] within Donabedian's[39] structure-process-outcome framework. Duffy[38] argues that a focus on quality health care in conjunction with caring (the relational component of healing) is necessary to improve the process and outcomes of health care in the United States. In this model, patient, provider and system level factors interact and affect the process and outcomes of health care. Patient, provider and system factors significantly affect the process and outcomes of obstetric care in the United States. The use of this model provides a framework for understanding which variables and outcomes to include in the research. Not all of the variables indicated in the framework will be included in this particular study; the framework is then a guide for next steps in the research (e.g., examining provider and system-level factors in the structure and outcome). Health disparities are rampant in U.S. obstetric care and the QCM provides an excellent framework for understanding how provider, patient and system factors might interact in the creation and perpetuation of health disparities. The QCM model was adapted with the author's permission.[40] "System relationships" was added to Process, based on findings from a literature review of provider management of the third stage of labor.

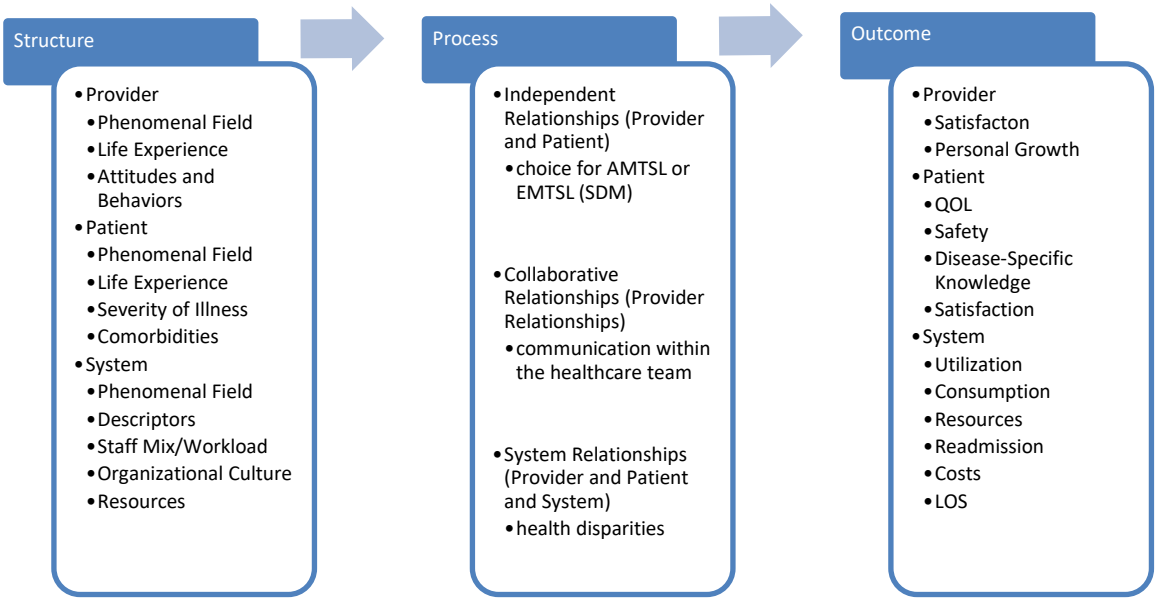


Fig. 1 Adapted Quality-Caring Model

Oxytocin Prevalence in US Obstetric Management and Its Association with Postpartum Hemorrhage and Primary Cesarean Section: A Scoping Literature Review

Introduction

Oxytocin is the hormone associated with labor contractions, milk let-down, orgasm and social bonding.[2] In synthetic form, oxytocin is one of the most powerful drugs in the obstetric pharmacopeia and one of only a few high-alert medications.[1,41] While oxytocin is the first choice for prevention and treatment of postpartum hemorrhage globally, it is also used to induce and augment labors, especially in high-resource settings. The benefits of oxytocin use in labor include shorter duration of labor[42,43] and the possibility of decreasing the rate of cesarean sections[43–48]. The adverse effects of oxytocin use in labor include postpartum hemorrhage,[31,36,49,50] uterine rupture[51], neonatal morbidity[47,52], cesarean section in low-risk women (secondary to fetal distress)[53–58], episiotomies[59] (and severe lacerations[60,61]) and breastfeeding difficulties[62–66]. There is also a growing body of literature examining the epigenetic effect of fetal oxytocin exposure[67,68], as well as the association of exposure with childhood development[69,70] and disease[71]. Many of these effects, or the extent of these effects, are still being debated due in part to the inconsistency of definitions and measurements, as well as the varying quality of the available research. This review will examine how oxytocin is being used to induce or augment labor, especially in high-resource settings, its measurement in research, and its association with a leading cause of maternal morbidity and mortality, postpartum hemorrhage, and a primary focus of quality improvement efforts, the reduction of primary cesareans in low-risk nulliparous women.

Methods

A literature search was conducted in PubMed, CINAHL, Web of Science and Embase (see Fig. 1). The search was limited to human-only studies conducted in the past 5 years and published in English. Additional articles were found by reviewing references, including pertinent research published in the last 10 years and one article written in English and French. The search terms used were "oxytocin labor" (MeSH terms were used in PubMed); this yielded 2840 results, of which 2,640 were screened. Of the titles screened, 256 were selected for abstract review; ultimately 41 articles were included in the literature review. The review was conducted as pharmacoepidemiology scoping review. Articles were included for review if they examined or discussed the prevalence of oxytocin use in the intrapartum in high-resource settings or if they examined the effects of oxytocin use on the population. Articles were excluded if they focused exclusively on oxytocin use in the third stage of labor or if they did not discuss oxytocin specifically. Therefore, if a study examined induction or augmentation, but not oxytocin specifically, it was excluded from the review. This decision was made because both induction and augmentation are heterogenous categories including an array of medications and procedures and, therefore, do not specifically reflect the prevalence or effects of oxytocin use. Literature and Cochrane reviews were eligible for inclusion. Mapping was used to extract the main themes in the oxytocin use literature to organize the presentation of results. The main themes included: use prevalence, exposure measurement, maternal and fetal/neonatal effects and safety. Several maternal and fetal/neonatal effects of oxytocin were identified in the literature. Postpartum hemorrhage and primary cesarean section outcomes were chosen because they are prevalent and intimately linked to the physiology of oxytocin and the rationale for its intrapartum use. "Safety" as a theme included research examining interventions to mitigate the amounts of oxytocin used

and its effects, litigation, staffing and inappropriate use of oxytocin. The use of oxytocin in labor without a medical indication was frequently mentioned in studies looking at oxytocin prevalence; other safety topics were not included in this review as they focused predominantly on changing the use of oxytocin to effect outcomes.

Results

41 studies were included in the final literature review. The studies were conducted in Europe, the United States, Australia, Canada, Turkey and South America (one study of hospitals in Uruguay and Argentina). 32 of the 41 studies were published in the last five years and most of the study data was collected in the 2000s-2010s. The majority of the studies were retrospective cohort studies, followed by some case-control and prospective cohort studies. Many of the studies were secondary data analyses of existing datasets. Three Cochrane and three literature reviews were also included in the current literature review.

Prevalence

In a review of the literature, secondary data analyses and a retrospective cohort study found variation in oxytocin use, but overall evidence indicates that around half of the women in labor in the United States will be exposed to exogenous oxytocin in labor and, therefore, most children born in the United States have been exposed to exogenous oxytocin in vitro.[41,72,73] No prospective cohort studies were found which examined the use of oxytocin in intrapartum management in the United States as their primary purpose. Of the seven studies mentioning the prevalence oxytocin use, none specifically examined oxytocin, but rather cesarean delivery levels [33,72], the impact of early admission on interventions[74], labor[35,73] and induction[75,76] patterns. These studies indicate that oxytocin is the most common drug used for induction and augmentation in the United States.[35,73,75] With regards to induction of labor, one study using the

Consortium of Safe Labor database (N = 638,802) found that, at minimum, 65.8% of nulliparous and 62.8% of multiparous women undergoing induction were exposed to oxytocin.[35(p486.e7)] A much smaller study of 848 women, found that 73.7% were induced primarily with oxytocin.[75(p407)] Of the studies examining cesarean section, one reported oxytocin use varying from 66-68.3%[72(p689.e3)] among 7,845 women at ≥ 37 weeks gestation with singleton, vertex pregnancies and no history of cesarean section; the other study of 2,851 nulliparous women with vertex, singleton pregnancies attempting vaginal birth reported 57.3% of the study sample was augmented with oxytocin[33(p7)] Two studies examined contemporary labor patterns in the Consortium on Safe Labor database (2002-2008) and reported oxytocin augmentation ranging from 31%[76] (of 98,359 women) to "nearly half" of 62,415 women[73]. Three of these studies used the Consortium of Safe Labor Database and reported very different numbers regarding oxytocin exposure based on their respective research question and primary outcomes and, therefore, sample composition.[35,73,76] One other study (N = 216) found that half of the nulliparous women in spontaneous labor in the study were augmented with oxytocin.[74(p31)]

In other high-resource countries, oxytocin use in the intrapartum is similarly common. Studies examining low-risk women in spontaneous labor found that overall oxytocin augmentation rates averaged between 40.5% - 58%.[77–79] The lowest reported oxytocin augmentation rate was 26.4% of an Icelandic cohort.[80] Low-risk nulliparous women in spontaneous labor had higher rates of oxytocin augmentation, ranging from a low of 32.4% in the Netherlands[81] to 43.8% in Norway[82] to 45.4% in Australia[83] to 52.6% in Germany[79] to 75% in Sweden[78]. Multiparous women who were low-risk were less likely to receive oxytocin augmentation in labor, but still had augmentation rates of 27%[79] – 38.1%[78].

Several studies indicate oxytocin is frequently used for augmentation without an appropriate indication, such as labor dystocia.[78,79,84,85] Such use is considered inappropriate. A Swedish and a German study examining the management of prolonged labor[84] and the sequence of labor interventions[79] in low-risk women, respectively, found that oxytocin was not always used appropriately. Of 829 women in spontaneous labor in the Swedish study, 28% received oxytocin augmentation without evidence of prolonged labor[84(p1)]. 40.5% of 3,055 low-risk women in the German study were augmented with oxytocin however not all of these met criteria for oxytocin augmentation.[79(pp249, 253)] Two further studies, in Norway[85] and Sweden[78], also concluded that oxytocin use for augmentation was not always appropriate. Of 747 low-risk nulliparous women in spontaneous labor in Norway, 42.5% of the 43.8% of women being augmented did not meet criteria for dystocia[85(p364)]. Of 1,263 women in spontaneous labor in Sweden, 55% received oxytocin augmentation, with women being over- or under-treated for dystocia.[78(p1353)] Similar studies have not been conducted in the United States, to the best of our knowledge.

Measurement

Oxytocin exposure is frequently measured as a binary variable.[6,35,90,91,46,74–76,86–89] Two studies conducted in 2011 introduced continuous measurement of oxytocin exposure via "total dose"[50] or "area under the curve"[36]. Total dose (milliunits, mU) is calculated by summing the products of each oxytocin infusion rate in milliunits/minute (mU/min) by the duration of that rate (min) for a given woman.[36(p56.e2),50] As a continuous measurement, total dose is difficult to interpret, so both studies created a categorical variable based on total dose. Belghiti et al[50]. used the 50th, 75th and 90th percentiles to create total dose categories; Grotegut et al.[36] examined total dose in 5000 mU

increments. In addition to total dose, Belghiti et al.[50] examined oxytocin as a binary variable and in terms of maximum infusion rate (mU/min) and total duration of exposure (min).

In 2015, three studies used different methods to measure oxytocin exposure: total dose (mU)[92], maximum infusion rate (mU/min)[93] and a comparison of maximum infusion rate at greater or less than and equal to 20 mU/min[94]. Both studies[93,94] that looked at rate did so in order to gather information to improve oxytocin protocols; none gave specific rationale behind the measurement method chosen. Two 2017 studies used a variety of methods for measuring oxytocin exposure: mean and maximum oxytocin infusion rate (mU/min), hourly and total oxytocin dose (IU and mU)[95] and the duration of each specific infusion rate as well as total duration (min) of oxytocin exposure (min)[96]. In 2018, two studies[97,98] used a variety of methods to measure oxytocin exposure. One study examined initial, average and maximum infusion rate, as well as duration, to examine the impact of instituting an oxytocin checklist on usage and outcomes.[97] The other study used maximum oxytocin rate (mU/min), total duration (h), oxytocin product (mU/min*h [sic]) and total dose (mU) in order to determine whether the product of maximum rate times total duration would be a good surrogate for total dose.[98(p79)] All of the studies were retrospective cohort, case-controls or secondary data analyses. While there is no agreement in the literature, yet, regarding categories for oxytocin infusion rate and total dose, both measures promise a more detailed understanding of the effect of oxytocin on outcomes of interest in a manner that is easily interpretable for clinical practice.

Effects

Postpartum Hemorrhage

Four studies[36,50,99,100] specifically examined the relationship of intrapartum oxytocin exposure to postpartum hemorrhage. A secondary data analysis conducted in South America,

examined oxytocin exposure as a binary variable and found no association between intrapartum oxytocin exposure and hemorrhage risk, if women also received active management of the third stage of labor.[100] A secondary analysis of 41,941 births in the United States measured oxytocin as a binary variable (i.e. maximum infusion rate was greater than 20 mU/min).[99] The study found that receiving a maximum infusion rate greater than 20 mU/min was an independent predictor of uterine atony.[99(pS86)] These findings were corroborated by a case-control study of 3,240 women in France which found that the odds of a severe postpartum hemorrhage increased significantly at a maximum infusion rate of 10-15 mU/min (compared to no oxytocin) and then increased significantly again for a maximum infusion of > 15 mU/min.[50(p4)] This same study also examined oxytocin exposure as total dose and found that the odds of severe hemorrhage, after adjusting for other variables, was three times greater for a total dose 2000-4000 mU and six times greater for a total dose above 4000 mU, compared to receiving no oxytocin.[50(p4)] Similarly, a case-control study of 108 women in the United State, 54 with and 54 without severe postpartum hemorrhage, found that, after adjustment and compared to no oxytocin exposure, every 5000 mU increase in total dose was associated with a 58% increase in the odds of having a severe hemorrhage.[36(p56.e5)]

A number of studies have examined oxytocin exposure and relationship with PPH as a secondary aim; all of these studies measured oxytocin exposure as a binary variable.[31,85,88,89,101] With one exception[101], these retrospective studies, conducted in Switzerland[89], Norway[85], Turkey[88] and France[31], found that oxytocin exposure statistically significantly increased the odds of experiencing a postpartum hemorrhage while controlling for other risk factors.

Two literature reviews[102,103] and a mini-Cochrane review[46] were retrieved during the search. The mini-Cochrane review, which was examining the effect of oxytocin augmentation in

women with epidurals on cesarean section rates and maternal morbidity, concluded that oxytocin exposure had "no effect on postpartum hemorrhage".[46(p760)] The review, however, only included two studies with a grand total of 319 women; 226 of the women in one study were fully dilated (difficult to study oxytocin augmentation in this sample) and 93 of whom were dilated ≤ 6 cm (arguably, therefore, not in active labor according to recent research[57,104]).[46(p760)] The largest of these reviews, which examined 43 studies to understand the maternal effects of oxytocin augmentation, concluded that "…oxytocin administration during spontaneous labor is associated with a higher risk of postpartum hemorrhage, especially when the dose used during labor is high, the increment intervals are short, or the woman does not receive prophylactic oxytocin immediately around delivery."[103(p516)] This review notes that the association between oxytocin exposure and postpartum hemorrhage has only been seen in observational studies, not randomized-controlled trials[103(p515)]. It would be exceedingly difficult to design a trial that would randomize women to receive oxytocin that would also be ethical. A scoping review conducted to understand whether induction or augmentation prior to cesarean section increases the risk of postpartum hemorrhage reported not finding enough research to answer the study question.[102] The researchers did find two studies, however, which indicated that oxytocin exposure prior cesarean was associated with higher postpartum oxytocin doses necessary to control bleeding, which would suggest that oxytocin exposure is associated with a greater risk of bleeding postpartum.[102]

Cesarean Section

The magnitude of the association between oxytocin exposure and primary cesarean delivery varies in the literature. The most common study findings were that oxytocin increased the risk of cesarean section or did not reduce the incidence of cesarean section.[48,58,83,85] Three studies found

that oxytocin exposure increased the risk of a cesarean section.[58,82,83] Two studies examined the introduction of oxytocin protocols and found that the implementation of such a protocol led to decreased numbers of cesarean sections.[44,56] One study found that oxytocin augmentation in nulliparous women with an epidural decreased the incidence of cesarean section; no mention was made of when oxytocin exposure started (i.e., before or after active labor).[105] In all of these studies, oxytocin was measured as a binary variable. Oxytocin alone, and as a component of active management of labor, has been examined as a means to reducing the length of labor and the number of cesarean deliveries, but it's dose-association with the incidence of primary cesarean sections in unknown.

Three separate Cochrane reviews found that, either: there was no statistically significant reduction in the use of cesareans caused by using oxytocin[48]; or, there was no increase in the number of normal deliveries[106]; or, that there was a small reduction in cesarean section, but that active management was "highly prescriptive and interventive"[107(p2)] for low-risk women. The Cochrane review of the active management of labor package which found a small decrease in cesareans included one-on-one nursing care.[107] The effect of one-one-one care, which is known to reduce analgesic requirements and cesarean rates, was not delineated from the effects of oxytocin.[107,108] The reviews were not able to take cervical dilation into consideration, and there is evidence that oxytocin exposure prior to active labor at 6 cm dilation may be a more significant risk factor for cesarean section, especially among nulliparous women, than oxytocin exposure at all.[57] A more recent review, conducted for the development of clinical guidelines in France, concluded that active management of labor did not decrease the incidence of cesareans and that the intervention should only be used for labor dystocia.[109(p541)]

Discussion

Oxytocin is a high-alert medication because of its potential to cause dose-association adverse outcoems.[1,57(p32)] Inappropriate use of oxytocin is noted in half of all paid obstetric litigation claims.[57(p33),108] The World Health Organization reports augmentation is needed in less than 30% of labors[110(pS270)]. In contrast, *most* women in the US and in other high-resource countries are exposed to oxytocin during labor. Studies from several European countries concluded that oxytocin is frequently used without an indication. A comprehensive understanding of how oxytocin is typically used in the US, including indication, quantification and timing, is not readily available. Preventive[57,97,111,112] or interventive[113–115] measures to decrease excessive use or misuse of oxytocin exist, but it is unclear to what extent they have been adopted.

Measurement is a persistent difficulty in the study of oxytocin. Many studies use "induction" or "augmentation" as variables, but both induction and augmentation are simply markers for an array of medications and procedures. When oxytocin is included as an independent variable, it is frequently a binary measurement[33,35,72–76]. Binary measurement of a continuous variable means that significant data is lost.

Recent studies have pioneered different measures, predominantly categorical, to better understand oxytocin use and its effects. There has been little methodological conversation, however, around the rationale behind these measures and which may be best pharmacologically, physiologically, or clinically. Several studies have used "total dose" to measure oxytocin with a variety of categorizations to aid interpretation. One key difficulty in summarizing these studies is a lack of consistent categorizations of the continuous variable (e.g., comparing percentiles[50] of oxytocin dose to 5000 mU increases[14]). Rationales for the categories researchers create are frequently not explicitly stated.[50] When rationales are given, they focus on choosing total dose

categories that the researchers think will result in significant results.[36(p56.e5),95(p383)] Researchers might consider using additional measures of oxytocin exposure that provide more information and greater clinical utility than a binary variable. Some examples include: total oxytocin dose (mU); maximum infusion rate (mU/min); and total duration (min) of oxytocin exposure. Further research is needed to determine the most effective measures of oxytocin exposure.

While there is some heterogeneity in the findings of these studies – due, in part, to the nature of the research questions and binary measurement of oxytocin – the overarching finding is that oxytocin exposure is an independent risk factor for postpartum hemorrhage. There is evidence that even two hours on a 20 mU/min infusion of oxytocin substantially increases the risk of severe postpartum hemorrhage, as does increasing the infusion rate above 20 mU/min [ref]. Further research is needed, however, to corroborate these findings, refine the understanding of oxytocin's association with hemorrhage (e.g., arrive at clinically relevant points in oxytocin exposure where risk for hemorrhage increases exponentially) and to translate these findings to inform clinical practice. One immediate suggestion, however, would be to include the potential increased risk for postpartum hemorrhage in providing informed consent to women around oxytocin use in labor.

To better understand the relationship between oxytocin exposure in labor and the risk of cesarean section, more detailed information about the use of oxytocin and its timing is needed. Since the majority of the extent literature on oxytocin's association with cesarean section measures oxytocin as a binary variable, little is known about its dose-association with cesarean section.

Conclusion

While frequent use of oxytocin in the intrapartum is documented in a variety of high-income countries, none of them have rates of maternal and neonatal morbidity and mortality as high as the United States. This suggests that while overuse or inappropriate use of oxytocin may contribute in part to morbidity and mortality outcomes, there are factors beyond its use that play a role. More research is needed regarding decision-making and communication around oxytocin use in the intrapartum period. Well-delineated definitions and measures are essential and may also require further research to develop.

Practice changes are needed to shift obstetric culture and how we use oxytocin. Two related foci for policy change are using the minimal amount of oxytocin necessary and addressing misuse of oxytocin (e.g., augmentation without an indication). Checklists, partograms and turning oxytocin off in active labor hold promise as ways to standardize the use of oxytocin, thereby improving maternal and neonatal outcomes.[41,56,57,97,111–116] Other potential interventions include one-on-one support, either with nurses or doulas.[117–119] The call for more judicious oxytocin use is not new[41], but it is time to act.

Figure 2: Literature Review Flow Diagram

PRISMA 2009 Flow Diagram[1]

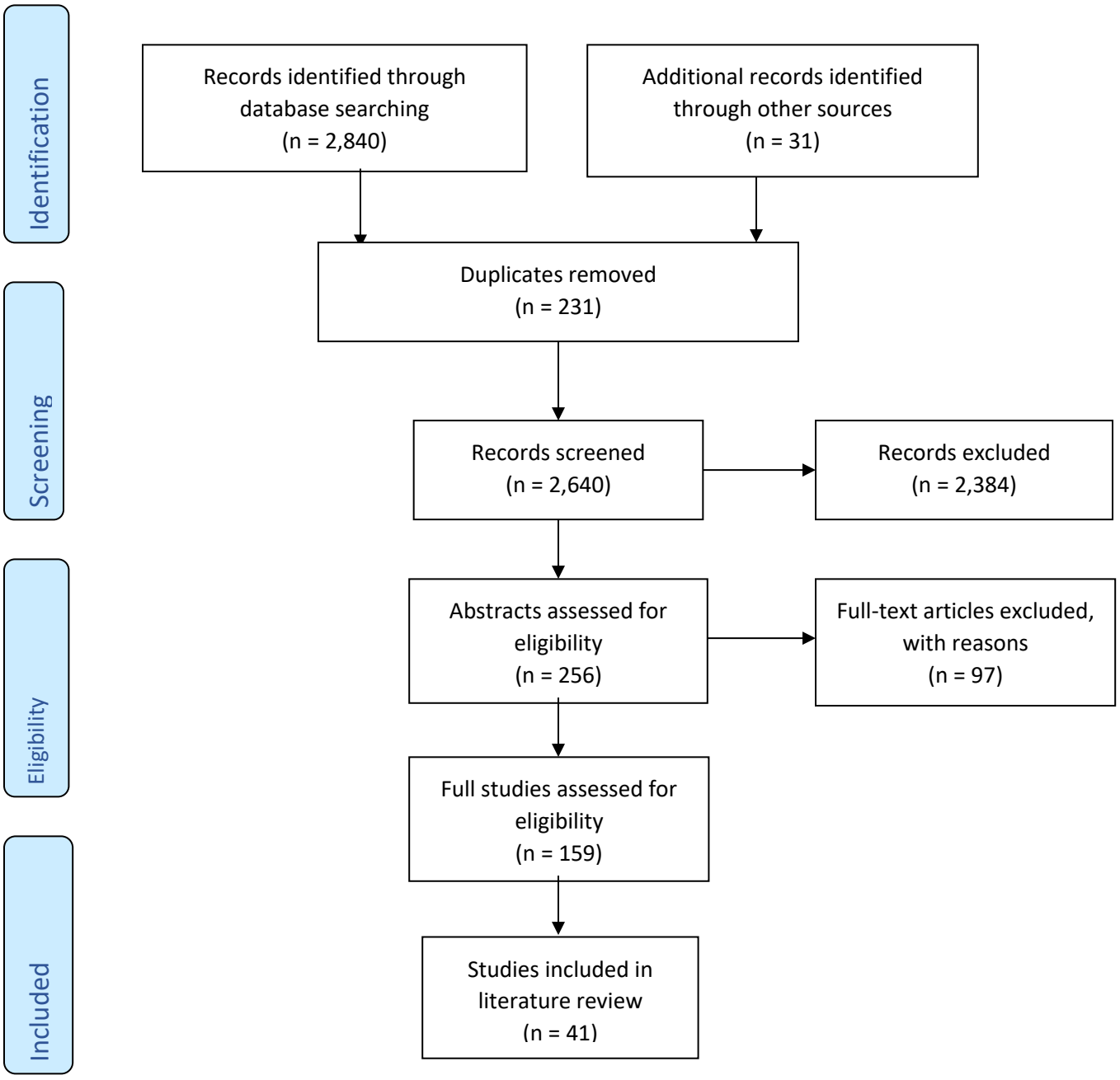


Figure 1 PRISMA Flow Diagram

[1] Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Table 1: Oxytocin Prevalence in Intrapartum Care

Author (Year)	Study Type and Purpose	Country & study population	Prevalence of oxytocin use
Laughon (2012)[35]	Retrospective cohort study (Consortium on Safe Labor) to describe labor induction (indications, methods and delivery mode) in the US	US (19 hospitals across the US); 208,695 women	42.9% of nulliparous and 31.8% of multiparous women were induced; 35.5% and 44.1% of these were elective[35(p486.e1)] Of those who were induced, at minimum 65.8% of nulliparous and 62.8% of multiparous women were induced with oxytocin alone (as the authors note, other methods of induction may have included oxytocin exposure)[35(p486.e7)]
Laughon (2012)[76]	Secondary analysis of two retrospective cohorts – Collaborative Perinatal Project from 1959-1966 and Consortium of Safe Labor from 2002-2008	US (CPP 39,491 women and CSL 98,359 women)	Oxytocin augmentation increased from 12% to 31%[76(p419.e2)] between the two cohorts
Nystedt (2014)[84]	Retrospective cohort examining prevalence, management and outcome of prolonged labor with normal labor	Sweden; 829 women with spontaneous labor[84(p1)]	28% were augmented with oxytocin without evidence of prolonged labor[84(p1)]
Petersen (2013)[79]	Prospective cohort study examining sequence of interventions with relation to length of labor and delivery mode	Lower Saxony, Germany; 3,055 low-risk women delivering in hospitals	Overall, 40.5% of women were augmented with oxytocin (52.6% of nulliparous, 27% of multiparous women)[79(p249)] "one may infer that oxytocin was not always applied

			appropriately in our study population"[79(p253)]
Belghiti (2013)[77]	(in French and English) Secondary Data Analysis of the French Perinatal Survey Data to estimate the frequency of oxytocin administration during labor – and characteristics of woman and hospital associated with its use	France; 14,681 women	64% of laboring women received oxytocin in labor; 58% of women with spontaneous labor received oxytocin[77(p663)] Factors increasing risk of oxytocin exposure: epidural, nulliparity, overweight, "private status", small maternity unit[77(p663)]
Tam (2013)[75]	Retrospective cohort study examining outcomes for elective induction of labor	US; 848 records	73.7% were induced with oxytocin as the primary agent[75(p407)]; shorter duration of labor noted
Bernitz (2014)[82]	Secondary data analysis of a randomized controlled trial examining the effect of oxytocin augmentation and birth outcomes	Norway; 747 low-risk nulliparous women	43.8% of the study population was augmented with oxytocin; 42.5% of these women did not meet dystocia criteria[85(p364)]
Selin (2009)[78]	Retrospective cohort examining use of oxytocin for augmentation and association with labor progress and delivery outcome	Sweden; 1,263 women at ≥ 37 weeks gestation in spontaneous labor with a single, vertex fetus	55% of women received oxytocin (75% of nulliparous, 38.1% of multiparous); oxytocin was used in a haphazard manner – women were over or under-treated[78(p1353)] Oxytocin use varies significantly by hospital[78(p1353)] Cesareans were related to underlying labor dystocia – not

			oxytocin (suggesting need for better decision-making tools)
Rosenbloom (2017)[72]	Secondary data analysis of a prospective cohort study conducted between 2010-2014 at the Washington University School of Medicine to examine effect of adopting the 2010 CSL labor guidelines to reduce cesarean	US; 7,845 women at ≥ 37 weeks with a vertex, singleton pregnancy and no history of cesarean	Oxytocin use varied from 66-68.3%[72(p689.e3)]
Buchanan (2012)[83]	Retrospective cohort study to examine intrapartum oxytocin use trends and associations with morbidity from 1998 to 2008	NSW Australia; 322,640 low-risk, nulliparous women with single, cephalic fetus	45.4% of women in the study were exposed to oxytocin – increase was due to increased use of induction Associated with increased maternal and neonatal morbidity; as well as epidural use, operative and cesarean delivery[83(p173)]
Neal (2014)[57]	Secondary data analysis from two prospective cohort studies conducted in three hospitals in the midwestern US to examine effect of admission in early labor on interventions	US (Midwest); 216 nulliparous women in spontaneous labor	142 of 216 nulliparous women in spontaneous labor received oxytocin augmentation[74(p31)]
Kjerulff (2017)[33]	Prospective cohort study of women delivering in Pennsylvanian hospitals between 2009-2011 examining risk factors for cesareans among nulliparous women	US (PA); N = 2,851 nulliparous women with vertex, singleton pregnancy attempting vaginal birth	30.1% of women induced with oxytocin, 57.3% of women augmented with oxytocin[33(p7)] Of 2,851 nulliparous women, 34.3% were induced – 69% of these were also augmented with oxytocin[33(p5)]

Zhang (2010)[73]	Secondary data analysis of the Consortium of Safe Labor Database (retrospective cohort study) to examine labor patterns in the US	US; N = 62,415 women	"nearly half of the parturients included in our analysis were given oxytocin for augmentation"[73(p5)]
Cheyney (2014)[120]	Retrospective cohort study of the Midwives Alliance of North America Statistics Project to examine outcomes (2004-2009)	US; 16,924 women	4.5% of the total population received oxytocin[120(p17)] 10.9% were transferred, 22% of these required oxytocin augmentation[120(p22)]
Offerhaus (2014)[81]	Secondary Data Analysis of the Netherlands Perinatal Registry to examine the rate of cesarean sections and other interventions in low-risk births (at home and in the hospital) – 2000-2008	Netherlands: 807,437 births	Of 39,747 nulliparous women in 2008, 32.4% were augmented; of 48,200 multiparous women in the same year, 7.8% were augmented (this was a significant increase from 2000 when 18.9% of 42,787 nulliparous and 4.5% of 48,882 multiparous women were augmented with oxytocin)[81(p651)] In 2008, 45.6% of nulliparous women who planned to deliver at home delivered in the hospital – of these, 19.1% received augmentation; 38.7% of multiparous women transferred, 9.3% of these received augmentation[81(p652)] (though it should be noted that some women delivering at

			home also received augmentation)
Halfsdansdottir (2015)[80]	Matched retrospective cohort study to examine outcomes of homebirth in Iceland (2005-2009)	Iceland; 307 home births to 921 planned hospital births	Overall oxytocin augmentation was 22% with 8.8% of planned home births receiving oxytocin and 26.4% of planned hospital births receiving oxytocin[80(p21)]

Table 2: Oxytocin Measurement

Author (Year)	Study type and purpose	Country and Study Population	Oxytocin measures	Authors' rationale for measure choices
Grotegut (2018)[98]	Secondary data analysis of a retrospective cohort study at Duke (2009-2010) and a French cluster randomized controlled trial (2004-2006) to examine whether max rate and duration could be a surrogate for the total dose of oxytocin received in labor	US and France; 402 and 6,907 women, respectively	-Maximal oxytocin rate (mU/min) -Total duration (h) -Oxytocin product (mU/min * min) -Oxytocin total dose (AUC) (mU) *Found significant correlation between max rate*tot duration and "total dose"	Oxytocin exposure is an important predictor of labor outcomes[98(p79)] Surrogate for total dose that is easier to calculate (p 79) (Not clear how this would be helpful during labor, though)
Roloff (2015)[92]	Retrospective cohort study of women delivering from May-July 2012 in a California institution to examine the cumulative oxytocin dose needed to achieve vaginal delivery among obese/non-obese women	US (California); 413 women	Total dose of oxytocin received in mU Time not considered	None given
Grotegut (2015)[93] Poster	Secondary data analysis of the Maternal-Fetal Medicine Units cesarean registry (prospective cohort) to examine whether max infusion rate is associated with	US; 41,941 women who experienced labor in the MFMU cesarean registry	Max infusion rate (mU/min) – max greater than 20 mU/min significantly associated with increased risk for atony	To modify oxytocin protocols to reduce max rate and thereby reduce risk of PPH (Used OR – not clear if appropriate)

	uterine atony as total oxytocin exposure			
Carlson (2017)[121]	Secondary data analysis of the University of Colorado Perinatal Database (retrospective cohort) between 2005-2012 to examine the effect of BMI, and other factors, on hourly doses of oxytocin	US (Colorado); 400 women (matched)	Duration Mean oxytocin infusion rate - "Rate across entire augmentation" mU/min[24(p388)] Total dose of oxytocin (mU) Hourly oxytocin dose (mU) – average – and then looked at how BMI affected this	Research has not found BMI to predict total dose of oxy in spontaneously laboring women – unknown whether BMI predicts the hourly oxytocin dose[121(p383)]
Grotegut (2011)[36]	Retrospective case-control study at Duke from 2000-2004 to compare oxytocin exposure in women with postpartum hemorrhage due to atony to women without	US (North Carolina); 108 women	"area under the oxytocin dose curve" defined as mu/min * min[14(p56.e2)] Looked at the increased OR of PPH over 5000 mU increases in oxytocin[14(p56.e5)]	No specific rationale given Looked at 5000 mU increases because this was believed to be more likely to have meaning clinical implications – no discussion of why 5000 mU
Frey (2015)[94]	Nested case-control study of a retrospective cohort study at a tertiary care hospital from 2004-2008 in order to examine characteristics associated with high maximum oxytocin dose	US (Washington); 108 cases and 2,864 controls	Cases = oxytocin > 20 mU/min, Controls = oxytocin <= 20 mU/min (associated factors: GDM, LGA, intrapartum fever, magnesium, IOL)	To identify women exposed to an oxy rate >= 20 mU/min to construct better oxy guidelines[94(p1614)]
Mohta (2018)[97]	Retrospective cohort study from 2012-2016 to assess the effect of an	US (California); 34,612 women	Initial infusion rate Max infusion rate Average infusion rate	To examine effect of intervention – which decreased oxytocin use on

	oxytocin checklist on usage and outcomes		Duration	all counts – also a decrease in NICU admissions and neonatal oxygen requirements
Maeder (2017)[96]	Retrospective cohort study from January-June 2013 to evaluate oxytocin titration for post-dated induction among different BMI groups	US (Midwestern university-affiliated hospital); 280 women (21 normal weight, 134 overweight and 125 obese)	Total oxytocin ("units")[96(p500)] Duration, hours Max infusion, mU/min Time between rate changes	Current dosing practices come from old studies that didn't look at BMI, but recent studies show BMI increases oxy dosage
Belghiti (2011)[50]	Secondary data analysis (nested case-control study) of a cluster randomized controlled trial (Pithagore6) to examine the association between oxytocin exposure in labor and risk of severe PPH	France (2004-2006); 3,238 (1,483 women were cases and 1,758 women were controls)	Binary Total dose (IU) Max infusion rate (mIU/min) Total duration (min) Categorized to the 50th, 75th and 90th percentile	No specific rationale related to measurements

Table 3: Oxytocin and Postpartum Hemorrhage

Author (Year)	Study Type and Purpose	Country and Study Population	Maternal Effects	Measurement	Dose/Duration Associated with Outcome
Bernitz (2014)[82]	Secondary data analysis of a randomized controlled trial examining the effect of oxytocin augmentation and birth outcomes	Norway; 747 low-risk nulliparous women	Dystocia Women without dystocia had an increased risk of operative delivery and episiotomy if augmented with oxytocin[82(p364)] "at all three units oxytocin, to some extent, was given without indication" (365) Active labor was 3-4 cm (365) Odds of PPH stat significant for augmented but no dystocia compared to no dystocia and no augmentation (366) – both results disappeared in the full model (368)	Max dose was 30 mU/min Oxytocin measured as binary variable	N/A
Steinberg (2013)[46]	Mini-Cochrane review of two studies to examine whether oxytocin	2 studies; 319 women (226 fully dilated	Oxytocin augmentation/CS "Oxytocin does not reduce the frequency	Binary	N/A

	augmentation in women with epidurals decreases operative deliveries and morbidity	and 93 ≤ 6 cm dilation[46(p760)]	of cesarean delivery, instrumental vaginal delivery … no effect on postpartum hemorrhage"[46(p760)] *Not sure that their sample population was appropriate, given their research question		
Grotegut (2011)[36]	Retrospective case-control study at Duke from 2000-2004 to compare oxytocin exposure in women with postpartum hemorrhage due to atony to women without	US (North Carolina); 108 women	Oxytocin and PPH Case group had mean oxytocin AUC of 10,054 mU, compared to mean to 3,762 mU in controls (mean might not be best choice, as oxytocin right skewed – median a better choice) Case and control groups not exactly equivalent – far more pre-eclamptics (and more likely to be exposed to mag) in case group and race/ethnicity groups differ; also, had lower hematocrits[36(p56.e3)]	"area under the concentration curve" (mU/min*min) = also total oxytocin dose Total time of infusion Time from infusion to delivery (min) Max oxytocin infusion (mU/min) Time from max rate to delivery (min) Oxy dose at delivery (mU/min) Oxytocin on at delivery Max infusion on at delivery	Dose/duration associated with outcome – used 5000 mU intervals After adjusting, OR was 1.58 and stat significant (For every 5000 mU increase, odds of severe PPH increased by 58%)[36(p56.e5)]
Sosa (2011)[100]	Secondary data analysis of a retrospective cohort study to examine the	Argentina and Uruguay; 11,323 women	No association between oxytocin exposure and mod/severe PPH or	Binary variable	N/A

	association of intrapartum oxytocin exposure on PPH in women receiving AMTSL	with vaginal deliveries	transfusion in the 36% of women who received AMTSL[87(p238.e1)] 6991 of 11,323 women were exposed to oxytocin in labor (238.e2) A lot that was not adjusted for in overall model (238.e4)		
Ekin (2015)[88]	Retrospective cohort study to identify risk factors and etiology of severe PPH[88(p1249)]	Turkey (2011-2014); 536 women with PPH	Oxytocin augmentation statistically significantly increased the odds of severe PPH (but about 25% of the study population had a severe PPH, so not sure OR is the best method for presenting the data) No discussion of how blood loss was measured; used blood loss ≥ 2000 mL as criteria of severe PPH	Binary variable	N/A
Bischoff (2017)[102]	Literature review to examine whether induction or augmentation of labor prior to CS increases the risk of PPH		PPH Dearth of research – most research looked at AMTSL without considering intrapartum	Binary	N/A

			oxytocin[102(p1)]; they found two studies that might provide further data, but these were not yet completed; they also found 2 studies looking at amount of oxytocin needed to prevent PPH after CS for arrest (10) – laboring women exposed to intrapartum oxytocin may require greater doses PP to prevent hemorrhage (10) – Belghiti 2011 and 2013		
Rousseau (2017)[103]	Literature review of oxytocin augmentation and its maternal effects * Beautiful table looking at oxytocin augmentation and risk of PPH (p 517-518)	43 studies	Mat risk and adverse effect Association between intrapartum oxytocin and increased risk of PPH seen in observational studies, not RCTs[103(p515)] – but, they conclude that "Overall, oxytocin administration during spontaneous labor is associated with a higher risk of PPH, especially when the dose used during labor	Grotegut and Belghiti were the studies mentioned who measured oxytocin in ways other than binary; also, Loscul et al looked at increment interval – but this was in French	N/A

			is high, the increment intervals are short, or the woman does not receive prophylactic oxytocin immediately around delivery."[103(p516)]		
Mehrabadi (2013)[6]	Retrospective cohort study to examine the etiology of the temporal increase in PPH	British Columbia, Canada (2001-2009); 371,193 women	PPH (not explained by IOL/AOL) Not able to explain the increase in PPH (had labor induction and oxytocin augmentation data – but not complete oxytocin data)	Binary – no dosing information available[101(p860)]	N/A
Khirredine (2013)[31]	Secondary analysis (case-control) of a cluster randomized controlled trial (Pithagore6) to examine association between labor induction and PPH in low-risk women	France (2004-2006); 4,477 low-risk women with PPH, 1,745 controls	Found that both oxytocin and prostaglandin inductions increased risk of PPH	IOL common, but OR used to report results – maybe not best statistical method More cases than controls Binary	N/A
Christmas (2016)[55] Poster	Retrospective cohort study to examine labor induction with cervical ripening (pharm or mech) versus oxytocin alone on incidence of PPH and CS	US (2014-2015); 29,678 women	Induction with ripening increased risk greater than oxytocin alone – esp. among nulliparous women	Binary Results reported as percentages; not specified if there was any control for confounding	N/A

Grotegut (2015)[93] Poster	Secondary analysis of the MFMU registry to examine whether max infusion rate was associated with uterine atony in like manner to total oxytocin	US; 41,941 women	Max infusion rate > 20 mU/min "independently predicted uterine atony"[99(pS86)]	Max oxytocin infusion rate	> 20 mU/min associated with increased atony
Kaelin Agten (2011)[89]	Retrospective cohort study conducted to examine incidence of PPH and risk factors	Switzerland (1993-2014); 739,444 women	Oxytocin augmentation was one of the factors with highest risk for PPH[89(p1)] IOL 19% in 2015; Oxytocin AOL 26.2% in 2015	Binary	N/A
Belghiti (2011)[50]	Secondary data analysis (nested case-control study) of a cluster randomized controlled trial (Pithagore6) to examine the association between oxytocin exposure in labor and risk of severe PPH	France (2004-2006); 1,482 low-risk women with severe PPH and 1,758 controls	73% of cases and 61% of controls exposed to oxytocin Oxytocin associated with significantly higher odds of severe PPH; this was modified (decreased) by receiving prophylactic oxytocin ** Active labor defined as 3 cm	Binary variable Total dose (IU) Max infusion rate (mIU/min) Duration (min) Categorized by 50th, 75th and 90th percentiles	Odds of severe PPH was 3x higher for total dose 2-4 IU and 6x higher for total dose > 4 IU; odds also increased with increasing max infusion – 2.2 for max rate of 10-15 mIU/min and 3.2 for max rate > 15 mIU/min[37(p4)] Prophylactic oxytocin did moderate the

					effect of intrapartum oxytocin in this study (4)

Table 4: Oxytocin and Cesarean Section

Author (Year)	Study Type and Purpose	Country and Study Population	Maternal Effects	Measurement	Dose/Duration Associated with Outcome
Hidalgo-Lopezosa (2016)[58]	Retrospective cohort study examining the effect of oxytocin exposure on maternal and neonatal outcomes	Spain; 338 women in spontaneous labor at a tertiary care center between 2011-2013	Increased cesareans, epidurals and intrapartum fever No effect on 3rd or 4th degree lacs (2 women total), epis (36 total) Of women in spontaneous labor – 51% received oxytocin[58(p3)]	Oxytocin measured as binary variable	N/A
Costley (2013)[48]	Cochrane review of oxytocin augmentation for reducing operative deliveries in women with an epidural	2 trials; 319 women	No statistically significant differences found between oxytocin vs not and outcomes – however the number of women in the two studies were so limited, more studies are required (2) Outcomes were CS and operative delivery; interventions were oxytocin vs expectant management	Likely binary	N/A
Begley (2014)[43]	Lit review examining outcomes in studies examining oxytocin		Outcome measures	Binary	N/A

	use for treating prolonged first or second stage				
Bernitz (2014)[82]	Secondary data analysis of a randomized controlled trial examining the effect of oxytocin augmentation and birth outcomes	Norway; 747 low-risk nulliparous women in spontaneous labor	Dystocia Women without dystocia had an increased risk of operative delivery and episiotomy if augmented with oxytocin[82(p364)] "at all three units oxytocin, to some extent, was given without indication" (365) Active labor was 3-4 cm (365) Odds of CS was stat significant (366) – but numbers were small	Max dose was 30 mU/min Oxytocin measured as binary variable	N/A
Brown (2013)[107]	Cochrane review to examine active management of labor (oxytocin, amniotomy and one-on-one care) for reducing cesarean section	6 trials; 5,390 low-risk women in spontaneous labor	AML associated with a small reduction in cesareans, but "highly prescriptive and interventive"[107(p2)]	Binary	N/A
Grunebaum (2013)[44]	Retrospective cohort study to examine cesarean section rate before and after	NYC, US (2004-2012); 45,655 women	Reduced cesarean section from 41.6% to 32.7% - postulate one possible reason is that	Institution of oxytocin protocol (1 mU/min increased by 1 mU/min no	N/A

	implementation of a low-dose oxytocin policy designed to decrease liability[44(p53)]		non-reassuring FHT is one of the main indications for CS in laboring women – tachysystole is a common effect of oxytocin which might lead to NRFHT (53)	more frequently than every 15 min – decrease or stop when tachysystole present) (51) Binary	
Christmas (2016)[55] Poster	Retrospective cohort study to examine labor induction with cervical ripening (pharm or mech) versus oxytocin alone on incidence of PPH and CS	US (2014-2015); 29,678 women	PPH and Cesarean Induction with ripening increased risk greater than oxytocin alone – especially among nulliparous	Binary – seems like they just looked at raw numbers, no control for confounding or regression?	N/A
Rossen (2016)[56]	Prospective cohort study to examine implementation of an oxytocin protocol and whether the protocol would change the profile of oxytocin use and outcomes	Norway (2009-2013); 20,227 women	Oxytocin augmentation decreased from 34.9 to 23.1%[56(p355)]; found overall decrease in cesareans and decrease in cesareans for fetal distress[56(p355)] – on p 358, emergency cs very labile, not clear downward trend – also, labor >12 hr increased; severe PPH incidence increased (visually estimated)	Protocol was 6 mU/min, increased by 3 mU/min every 15 min to max of 40 mU/min (AMTSL with 5 IU oxytocin) P 357 for oxytocin use in study population – in 2014, 34.4% of nullips in spontaneous labor exposed to oxytocin Binary	N/A

Rossen (2018)[105]	Case control study to examine the effect of oxytocin augmentation, epidurals and maternal age (age being the primary predictor) on cesarean section	Norway and Denmark (2000-2011); 416,386 nulliparous women in spontaneous labor	Cesarean Oxytocin augmentation in nulliparous with an epidural associated with reduced risk of cesarean Did not mention cervical dilation	Binary	N/A
Buchanan (2012)[83]	Retrospective cohort study to examine intrapartum oxytocin use trends and associations with morbidity from 1998 to 2008	NSW Australia; 322,640 low-risk, nulliparous women with single, cephalic fetus	CS etc. Overall oxytocin use increased from 45.4% of all births in 2008, mostly due to inductions; was associated with an increase in CS (only looked at raw numbers) and severe maternal morbidity OR	Inclusion or exclusion in the model was determined based on statistical significance (not the best choice) Binary	N/A
Neal (2014)[57]	Secondary data analysis from two prospective cohort studies conducted in three hospitals in the midwestern US to examine effect of admission in early labor on interventions	US (Midwest); 216 low-risk nulliparous women	Admission prior to active labor in nulliparous women increases likelihood of oxytocin exposure and cesarean section 52.8% of women were admitted before active labor – 84.2% of these received oxytocin augmentation (compared to 45.1%	Binary	N/A

			of women in active labor – OR = 6.5) and 15.8% had a cesarean, compared to 6.9% of women admitted in active labor		

Oxytocin Use and Its Association with Postpartum Hemorrhage and Primary Cesarean Section in the US: A Study Protocol

Introduction

Oxytocin is a peptide hormone associated with orgasm, labor contractions, milk let-down, social bonding and stress reduction.[2,122] Centrally, oxytocin is made in the hypothalamus and secreted by the pituitary gland; peripherally, it is made by a variety of organs, including the placenta.[18,123] Oxytocin in its synthetic form is commonly used in obstetric practice to induce or augment labor, as well as prevent or treat postpartum hemorrhage (PPH). Induction, the stimulation of labor prior to its spontaneous onset, is considered when the benefits of delivery outweigh the risks of continuing the pregnancy.[124] Augmentation is the stimulation of contractions when the presence of the same has not resulted in progress in labor, measured by cervical dilation or fetal descent.[125]

Postpartum hemorrhage is a leading cause of maternal morbidity and mortality.[3] While maternal mortality rates have decreased globally, severe maternal morbidity has continued to increase.[126,127] Rates of atonic PPH, the most common type of PPH have increased in a number of high-resource countries.[4–11] The rate of PPH in the US is estimated to be 2.9%; but it accounts for 19.1% of in-hospital deaths after birth and is one of the most common causes of intensive care unit admission.[10] Morbidity related to PPH is significant and may include outcomes ranging from anemia and difficulty breastfeeding to loss of fertility, postpartum depression and post-traumatic stress disorder.[12,13] Observational studies in the United States have found that patient risk factors for PPH explain little of the rise in atonic PPH.[4,5,8,10,11] Most of these studies have used the National Inpatient Sample, which provides demographic data and International Classification of Disease (ICD) codes; the ICD, however, does not contain all codes pertinent to

PPH risk.[5,8,10,11] Specifically, the ICD does not contain codes for labor augmentation and, especially, for either induction or augmentation performed with synthetic oxytocin. Exposure to synthetic oxytocin in labor is an established risk factor for atonic PPH[14–16] and the extent of synthetic oxytocin use in obstetric practice may be increasing.[17,18] Oxytocin use is also associated with another significant maternal outcome and focus of quality initiatives, the primary cesarean section.[19–22]

Currently, 32% of births in the United States are cesarean sections.[23] Cesarean sections are considered major abdominal surgery and the procedure is associated with a number of adverse outcomes, including an increased risk for hemorrhage, infection, neonatal respiratory distress and complications with future pregnancies.[24,25] Reducing primary cesareans in low-risk women is a quality indicator for the Center for Medicare and Medicaid Services' Obstetric Core Measures, as well as a Healthy People 2020 goal and an initiative for the American College of Nurse-Midwives and the American Congress of Obstetricians and Gynecologists[25–28]. Oxytocin use is an independent risk factor for cesarean sections.[19–22,29]

Background

While it is estimated that 23% of births in the US are induced, there is evidence that this might be an underestimation, with rates of induction closer to 40%.[35,128] No billing code exists for augmentation, but it is estimated that 24% to 66% of births in the US are augmented.[33,35,73] Induction and augmentation of labor are independent risk factors for PPH.[8,30–32] Induction is an independent risk factor for primary cesareans.[19–22] Oxytocin is commonly used for both induction and augmentation and its use is associated with an increased risk of postpartum hemorrhage and primary cesarean section.[14,16,48,83,85] Induction and augmentation, however, cover a wide array of procedures and medications governed by varying policies.[33–35] For

instance, induction of labor may be performed with mechanical dilators, such as a Foley catheter, or with medications, such as methergine. Procedures to augment labor include artificial rupture of membranes and oxytocin administration. Although oxytocin is a high-alert medication[1] and there is evidence that more than half of laboring women in the United States are exposed to it[33,41,72,75,91], little is known about how it is used. In order to address the high rates of PPH and primary cesareans, in order to improve the quality of obstetric care in the United States, in order to improve maternal and neonatal outcomes, oxytocin use must be better understood.

This study examined the use of synthetic oxytocin in obstetric practice and its association with postpartum hemorrhage and primary cesarean section by using a nationwide sample of hospitals with inpatient obstetric units. To accomplish this purpose, the study: 1a) examined the incidence of synthetic oxytocin exposure in women admitted for labor in a large nationwide sample of hospitals; 1b) among women who received synthetic oxytocin, described synthetic oxytocin exposure via "total dose" by indication, as well as patient-, provider and hospital-level variables; 2a) examined the relationship between synthetic oxytocin exposure and postpartum hemorrhage accounting for patient-, provider- and hospital-level variables; 2b) for those that received synthetic oxytocin, examined the relationship between amount received as measured by "total dose" and postpartum hemorrhage accounting for patient-, provider- and hospital-level variables; 2b.1) explored whether there is a clinically-relevant point of oxytocin exposure associated with the risk of PPH; 3a) examined the relationship between the receipt of synthetic oxytocin and unscheduled cesarean accounting for patient-, provider- and hospital-level variables; 3b) for those that received synthetic oxytocin, examined the relationship between amount received as measured by "total dose" and unscheduled cesarean accounting for patient-, provider- and hospital-level variables; and 3b.1) explored whether there is a clinically-relevant

point of oxytocin exposure associated with the risk of a primary, unscheduled cesarean section. The study's a priori hypotheses were that: 1) the majority (i.e., > 50%) of hospital labors observed would include synthetic oxytocin exposure and the primary use of synthetic oxytocin will be for labor augmentation; 2) increased dose and duration of synthetic oxytocin would be associated with higher risk of PPH among women treated with this intervention, independent of patient characteristics; and 3) oxytocin exposure would be positively associated with the occurrence of primary, unscheduled cesarean sections, while accounting for patient-level variables.

Methods

This study is a secondary data analysis of the Consortium on Safe Labor, a publicly-available database housed at the Eunice Kennedy Shriver National Institute of Child Health and Human Development.[129]

Sample

Women admitted to the hospital for delivery, who were not admitted for a pre-labor cesarean, were considered at-risk for oxytocin exposure and were included in the study. The study sample was developed from the Consortium on Safe Labor, which was initially developed to examine patterns in labor progression and the etiology of frequent cesareans in the United States.[129] The study collected a large number of variables, including, but not limited to: maternal demographics, maternal medical and obstetric history, current pregnancy information, labor progress and outcome, medication administration (especially oxytocin), neonatal data, provider and hospital information. Data was collected from 19 hospitals, representing the American Congress of Obstetricians and Gynecologists' nine districts, via medical chart abstraction.[129] The database includes information about 228,562 births that occurred between 2002-2008.[129] Patient

information was de-identified before being sent to the Data Coordinating Center and is available to researchers upon request.[129]

Inclusion and Exclusion Criteria

Sites were included if they collected oxytocin data. Of the original 12 sites, 9 (75%) collected oxytocin data. These nine sites became the overall study sample, for a sample size of 182,742 births (147,981 unique women). Five sites were ultimately kept in the oxytocin dose data-set, for a sample size of 54,456 births (51,639 unique women). Women were excluded from the study if they were admitted for a scheduled cesarean since they would, theoretically, not be at-risk for oxytocin exposure. Of the 182,742 study participants, 20,541 (11.2%) were excluded for having a pre-labor cesarean section. All other women admitted to sites that collected oxytocin data were included in the study.

Sample size and power analysis

Postpartum hemorrhage incidence, based on ICD-9 codes, is estimated to be 2.9% in the United States.[130] In the study sample, 3% of the study sample had an ICD-9 code for PPH. Meanwhile, 3.1% of the study sample received a postpartum blood transfusion (about half of the women in the sample are missing data for this variable) and 12.3% of the population had a hemorrhage by estimated blood loss and delivery mode (i.e., greater than 500 mL of blood lost in a vaginal delivery; greater than 1000 mL of blood lost in a cesarean delivery).

A power analysis was conducted for the first part of the second aim, examining the association between oxytocin exposure in labor and postpartum hemorrhage. Assuming the frequency of oxytocin exposure among women admitted for labor is around 50% and that the rate of postpartum hemorrhage is 5%, an N of 4000 would be required to have 80% power, given

a significance level of 0.05, to detect an odds ratio (OR) of 1.46 for oxytocin as a predictor of PPH. Rates of postpartum hemorrhage vary; 5% was based on a sample from Johns Hopkins Hospital and is a little higher than some estimates (2.9%)[130] and a little lower than others (6-11%)[131]. Based on the literature, the adjusted OR (aOR) of 1.52 reported by Khirredine et al.[31] provides the best estimation of the risk of PPH after vaginal delivery given oxytocin exposure; the OR is likely to be higher (as evidenced by Al-Zirqi et al.[32]) if the delivery type is cesarean.

An additional power analysis was conducted for the second part of the second aim, examining the relationship between specific oxytocin dose exposures and postpartum hemorrhage. Oxytocin total dose means and standard deviation for women with and without PPH from Grotegut et al.[14(p56.e4)] were used to estimate the effect size of differing oxytocin dose exposures on the outcome of postpartum hemorrhage. Grotegut et al.[14] found a 1.58 increase in the odds of PPH for every 5000 mU increase in oxytocin dose. With an N of 2000 and given a significance level of 0.05 and a 5% PPH incidence rate in the population, the analyses would have 88% power to detect an odds ratio of 1.58 for oxytocin doses as predictors of postpartum hemorrhage.

Finally, a power analysis was conducted for the third aim, examining the association between oxytocin exposure and primary cesarean section. Assuming the frequency of oxytocin exposure is 50%[41] and that the rate of primary cesareans is 26.9%[128] (Zhang et al[45] found primary cesarean rates of 31.2% for nulliparous and 9.4% for multiparous women in the CSL data), an N of 3400 would be required to have 80% power, given a significance level of 0.05, to detect an odds ratio of 1.28 for oxytocin as a predictor of unscheduled cesarean sections. In the literature, the adjusted odds ratios for having the outcome of a cesarean, given an induction of labor (not, specifically, oxytocin exposure), are commonly greater than 1.32. Seyb et al.[19]

reports an aOR of 1.89 for elective inductions and 1.69 for medical inductions; Heffner et al.[20] reports an aOR of 1.7 for nulliparous women being induced and 1.49 for multiparous women being induced; Yeast et al.[21] reports an aOR of 1.75 for induced nulliparous women and 1.31 for induced multiparous women; and Caughey et al.[22]reports an aOR range of 1.33-1.92 for induced nulliparous women and 0.76-1.57 for induced multiparous women. There are no data on AUC and unscheduled cesarean section in order to conduct a power analysis for Aim 3b. Based on the power analyses for each of the specific aims, a minimum sample size of 4000 women is needed. The power analysis was conducted on PASS 14.0.[132]

Measures

Oxytocin

Oxytocin exposure is typically measured as a binary variable; while this is the simplest approach, significant information about the exposure is lost. The amount of oxytocin a woman is exposed to varies for a variety of reasons related not only to the patient (such as body mass index, gestational age and expression of oxytocin receptors[2]), but the provider and hospital, as well. We used total oxytocin dose (the sum of the products of each oxytocin infusion rate multiplied by the exposure time, calculated for each individual woman) in milliunits as the primary measure of oxytocin, as it captures more information about oxytocin exposure than binary measurement. Due to the wide range of oxytocin total dose, and in order to increase clinical utility, an oxytocin total dose categorial variable was created based on the continuous variable. The total dose categorical variable started at 0 mU and increased by 600 mU increments (equivalent to one hour on an infusion of 10 mU/hr) and, in the last few categories, by 1200 mU increments (equivalent to one hour on 20 mU/min as fewer women were exposed to these higher doses). The infusion rate categorical variable was created based on the maximum oxytocin infusion rate a woman

received. The maximum infusion rate categories were based on typical oxytocin policy – 20 mU/hr and 40 mU/hr – with 10 mU/hr being added in order to assess "low-dose" exposure. The binary measure of oxytocin exposure (i.e., yes/no) was used initially to enable comparison the study results with other studies that only use a binary measure.[14,93] Maximum oxytocin infusion rate (mU/min) provided a second measure of oxytocin exposure.[16,99] Stratifying women by the maximum infusion rate received provides more information than binary measurement and offers a simple clinical cross-over if typical protocol maximum infusion rates are used.[99]

PPH

The outcomes variables are postpartum hemorrhage (PPH) and primary cesarean. Only early PPH will be included, as, hemorrhage occurring in the first 24 hours after birth is more common and more likely to be associated with an atonic uterus and, hence, oxytocin exposure. Diagnosis of postpartum hemorrhage is complicated by inaccuracies in blood loss measurement, which is normally estimated visually and tends towards underestimation. Estimated blood loss may also be calculated by weighing or measuring, but both of these methods may be inaccurate due to the inclusion of other fluid (e.g., amniotic fluid or urine). Nevertheless, estimated blood loss is important because it is the primary method for diagnosing postpartum hemorrhage clinically. Hence, postpartum hemorrhage is likely underdiagnosed. In order to improve the identification of PPH, it will be defined in the following ways: a) postpartum hemorrhage diagnosis code (ICD-9 code) will provide the primary diagnosis of PPH; in the absence of a PPH diagnosis code, PPH will be diagnosed by: b) estimated blood loss (mL) with $\geq$ 500 mL and $\geq$ 1000 mL will indicate a PPH for vaginal or cesarean delivery, respectively and c) transfusion, emergent hysterectomy, manual removal of the placenta[16], uterine exploration[16], postpartum dilation and curettage, or use of methylergonivine, misoprostol, or carboprost. In the absence of estimated

blood loss and the presence of one of the above listed scenarios, a hemoglobin change of greater than 2 g/dL will be used to diagnose PPH.[16]

Cesarean

Cesarean section will be identified by ICD-9 code and recorded as a binary variable (yes/no). Women presenting for a scheduled cesarean (whether primary or repeat) are excluded from the study sample, therefore, cesarean deliveries in the study sample are ostensibly unplanned and represent either a primary cesarean or a failed trial of labor after a previous cesarean. The relationship between oxytocin total dose and primary cesarean sections will also be assessed.

Maternal Variables

Race/ethnicity, age, gestational age, parity and body mass index were collected from the labor and delivery admission form, as well as reproductive or medical history forms. Antenatal "large for gestational age" status was collected from the participant's prenatal history. Chronic and gestational diabetes, gestational hypertension, superimposed preeclampsia, severe and moderate eclampsia and eclampsia were all derived from the participants' charts. Chronic hypertension was based on an ICD-9 code and chart data, while magnesium sulfate and fever were both collected from the labor and delivery summary. Further detail about how variables were derived was not available. All of the maternal condition variables were binary. Race/ethnicity was categorical and included the following categories: White, non-Hispanic; Black, non-Hispanic, Hispanic, Asian/Pacific-Islander, Multi-racial and Other. Age, gestational age, parity and body mass index were all continuous variables.

Provider and Hospital Variables

Provider type (physician, midwife, physician-midwife team) was collected from the attending provider information on the delivery note. Hospital type, either teaching university, teaching community or non-teaching community hospital, was controlled for as an independent variable. Site was also controlled for. Site was the health system that participated in and contributed data to the Consortium on Safe Labor. Most sites only included one hospital (which varied by type), but one site included two different kinds of hospitals. Site likely represents system-specific policies and practice culture.

Recruitment and Data Collection

This was a secondary analysis of the Consortium on Safe Labor database. Data for the original study was extracted from electronic medical records by participating sites and recorded on a data extraction form.[133] Data extraction was coordinated by the "Data Coordinating Center" (DCC) which provided retrieval and transfer support.[133] Patient identifiers were removed prior to data transfer, except for dates which were re-coded by the DCC.[133] After data was transferred, the DCC prepared the database for analysis, including running audits on charts selected by an algorithm which sampled randomly and identified critical records requiring closer query.[133]

Most of the variables were collected in one central database, but oxytocin dosing and cervical exams for individual study participants were recorded in two separate databases. For the purpose of this study, the oxytocin database was merged with the central database by matching the participant identification number and entry number, since some women entered the study multiple times with subsequent pregnancies.

Analysis Plan

The demographic profile of the study sample was summarized with mean and standard deviation, frequencies and percentages, or median and interquartile range, depending on the distribution of

the variable. Descriptive statistics will also be provided for the Sites included in the study sample. Data will be examined for significant outliers. Statistical significance will be set at $p \leq 0.05$.

To examine the incidence of oxytocin exposure, overall incidence and the corresponding 95% Confidence Interval (CI) was presented. Exposure was then presented in terms of indication (induction vs. augmentation), patient, provider and hospital characteristics via incidence and corresponding 95% CI. Among women who received oxytocin, exposure was described by total dose, maximum infusion rate (by category and continuous) and time in hours and reported as median and interquartile range (IQR), stratified by indication, patient characteristics and hospital type. Patient characteristics included: indication (induction; augmentation), patient age (<20, 20-34; ≥35), race (non-Hispanic white/Caucasian; non-Hispanic Black/African-American; Hispanic; Asian/Pacific Islander), BMI (<18.5; 18.5-24.9; 25-29.9; 30-34.9, 35-39.9; ≥ 40), gestational age in weeks ($<36^0$; 36^0-37^6; 38^0-41^6; $\geq 42^0$) and parity (0; 1-4; ≥5).

Multivariable logistic regression was used to examine the relationship between the receipt of oxytocin and postpartum hemorrhage accounting for patient-, provider- and hospital-level variables. Clustering of women was managed by controlling for site. Participant entry, as some women re-entered the study with subsequent pregnancies, was also controlled for to handle the violation of the assumption of independence of observations, since women could enter the study more than once. Oxytocin exposure was initially measured as a continuous variable and then as a categorical variable (total dose categories and maximum infusion rates). PPH was outcome predicted by oxytocin, age, race, parity, gestational age, body mass index, gestational diabetes, diabetes, chronic hypertension, gestational hypertension, hypertension with super-

imposed pre-eclampsia, mild pre-eclampsia, severe pre-eclampsia, eclampsia, magnesium therapy[36(p56.e4)], labor dystocia, delivery mode, multiple pregnancy, macrosomia, maternal fever, entry into the study, provider-type, hospital-type and site number. Exploratory analyses were conducted to examine various thresholds of oxytocin exposure for association with PPH. A logistic regression was run with an oxytocin dose categorical variable; oxytocin dose categories increased by 600 mU (representing exposure to 10 mU/min for one hour) until the last 3 categories which increased by 1200 mU. After the regression was run, categories that were statistically significantly associated with increased odds of postpartum hemorrhage (and statistically different from each other) were used as oxytocin dose categories representing thresholds of increased risk. The same set of analyses, excluding delivery mode, was used to examine the relationship between the receipt of synthetic oxytocin and primary cesarean section.

Finally, the regression model was used to predict the probability of oxytocin exposure, and of postpartum hemorrhage and primary cesarean, in the study sample, while controlling for potential confounding variables as listed above.

Missing Data

Within the oxytocin data set, observations were dropped if the time variable was negative, missing or "0", which resulted in a sample size of 78,217 from 78,571. If the time variable was negative, it indicated postpartum oxytocin exposure, which was not of interest for the study. If the time variable equaled 0, 89.95% of the time, the dose variable was 0 or missing. Dealing with missing time was a challenge, due to the exceedingly wide range of exposure times, however, there was no reliable way to impute this time. 42% of the oxytocin doses associated with missing time were also missing (listed as "6666" or "9999"). There were 6,133 valid oxytocin doses,

ranging from 0-36 mU/min, associated with a missing time and all of these were from Sites 48 and 49.

Nine hospitals collected any oxytocin data and were included in the overall sample (see Figure 3). Of the nine sites, four were dropped. Three were dropped for having no oxytocin doses and one was dropped because 91% of the oxytocin doses were missing. Of the five remaining sites, one was missing 70% of the oxytocin doses, another was missing 17% and the remaining three were missing 2% or less of the oxytocin doses. Unknown oxytocin doses resulted in the observation being dropped as, again, there was no reliable way to impute these numbers.

In the sample, of all of the variables used in the model, only four were missing data. Those four variables were provider type (791 missing data), BMI (1,837 missing data), maternal age (200 missing data) and parity (1 missing datum). Among the sub-sample of women with recorded oxytocin doses, there were 34 missing data for provider type, 734 missing data for BMI and 8 for maternal age. In addition, there were 543 missing oxytocin total dose data; this is likely due to participants missing an oxytocin dose or time. Stata Statistical Software: Release 15 was used to conduct statistical analyses of the data.[134]

Sensitivity Analysis

Sensitivity analyses were conducted to examine the effect of changing the definition of postpartum hemorrhage on the outcome of the regression. Two different regression models were run, replacing PPH as identified by ICD-9 code with estimated blood loss at birth and postpartum transfusion status. In a similar manner, three different measures of oxytocin exposure were used as the dependent variable in the regression model – binary (yes/no exposure to oxytocin), total oxytocin dose (mU) and maximum oxytocin infusion rate (mU/min).

Discussion

This study significantly advanced the measurement of one of the most powerful – and common – medications used in labor. Categories of oxytocin total dose exposure in this study were smaller than in other studies and were created to be translatable for clinical understanding (i.e., categories were based on a 10 mU/min infusion rate over an hour). This study is innovative in its use of predicted probability to interpret the regression models.[135] Oxytocin's dose-specific association with primary cesarean section has not been previously studied, so this research provides preliminary findings for an aspect of obstetric care that is the subject of many quality improvement initiatives. At least two other studies examine oxytocin dosing in relation to the outcome of postpartum hemorrhage.[14,16] This study corroborates the dose-association of oxytocin with PPH (e.g., the risk of PPH seems to increase around 5000-6000 mU of oxytocin exposure), as well as an infusion-rate association.[14,16] Birth outcomes are complex, with numerous factors at play; this research will inform future studies to refine the measurement of oxytocin (including during its use in "real time") and the understanding of its many effects to change how it is used and improve maternal health care and outcomes.

While the analysis plan was created prior to receiving the Consortium on Safe Labor data, significant adjustments were made after receiving the data set, based on the available information and upon further consideration of statistical methods. Since the prevalence of oxytocin exposure and primary cesarean section are high, the odds ratio does not approximate relative risk well.[136] Odds ratios are also not easy to interpret.[137] Predicted probabilities based on the regression models were created to better understand and approximate the risk of the outcomes of interest.[135]

One of the biggest challenges was the measurement of oxytocin. The initial plan was to analyze oxytocin dose as a continuous variable. When the analysis was conducted, the large range of doses and the positive skew of the distribution rendered the analysis difficult to interpret. By looking at total dose over hour increments, points where the probability of hemorrhage or cesarean increased significantly were noted. Total oxytocin dose is a newer method of measurement[14,16] and one that holds promise for understanding clinically relevant points of exposure to oxytocin as it relates to potential adverse outcomes. The use of total dose in this research will not only allow a more nuanced understanding of oxytocin's effect on important measures of morbidity and quality care but will also contribute to the science regarding the use of this method for future research.

Presence of an ICD-9 code for postpartum hemorrhage was the primary indicator of hemorrhage. Estimated blood loss at birth, measured continuously in milliliters, was used to analyze the sensitivity of the hemorrhage definition. Other potential markers of hemorrhage, such as postpartum hemoglobin or receiving postpartum uterotonics apart from oxytocin, were not available in the data set. A variable for transfusion was available, though data was missing on more than half of the sample. Discrepancies in the data set indicated problems with the clinical diagnosis of hemorrhage. For instance, most women who received a postpartum blood transfusion were documented as losing less than 500 mL in a vaginal birth. Despite these difficulties, the use of three different definitions of hemorrhage and the use of sensitivity analyses is fairly detailed and similar to the triangulation methods used in other studies[15,16].

As in any study, and especially in a secondary data analysis, missing data was a concern. Initially, the plan was to examine the data (specifically, the oxytocin data) for patterns of "missing-ness" and then, potentially, to drop missing observations. While this is a relatively

unrefined method of dealing with missing data, and one that might be a source of unaccounted bias, substituting an "average" would have skewed the results of the analyses. Per the power analysis, despite dropping missing observations, there was still a sufficient sample size to examine the events of interest. Further, relatively little oxytocin data was missing from the five sites that were eventually included in the oxytocin analysis. Despite this, bias is still a concern. Women who were missing data were not noted to be systematically different on a patient-level, but the fact that only certain sites contributed oxytocin data and that these sites were different from each other (see Appendix 1) might contribute bias to the results.

Limitations

The study involves the secondary analysis of the Consortium on Safe Labor (CSL) database; as such, the collection of the research was not informed by this study's specific research question and the data was not collected by the authors. As a result, while the CSL contains most of the variables of interest, there were some pertinent variables (e.g., diagnosis of labor dystocia) that were not available for analysis. A related example is that not all the variables which were intended to help define which women sustained a postpartum hemorrhage were available, such as postpartum hemoglobin. The sensitivity analyses that were run as part of the study, however, helped confirm that most women with a postpartum hemorrhage were captured. A similar issue occurred with a measure which indicated whether a woman had a pre-labor cesarean. The variable was not a perfect marker for a pre-labor cesarean, however, as some women who were marked as having a pre-labor cesarean were also noted to have labored or received oxytocin prior to their cesarean. The decision was made to use the pre-labor cesarean variable as a marker, however, in order to remain consistent with the data codebook.

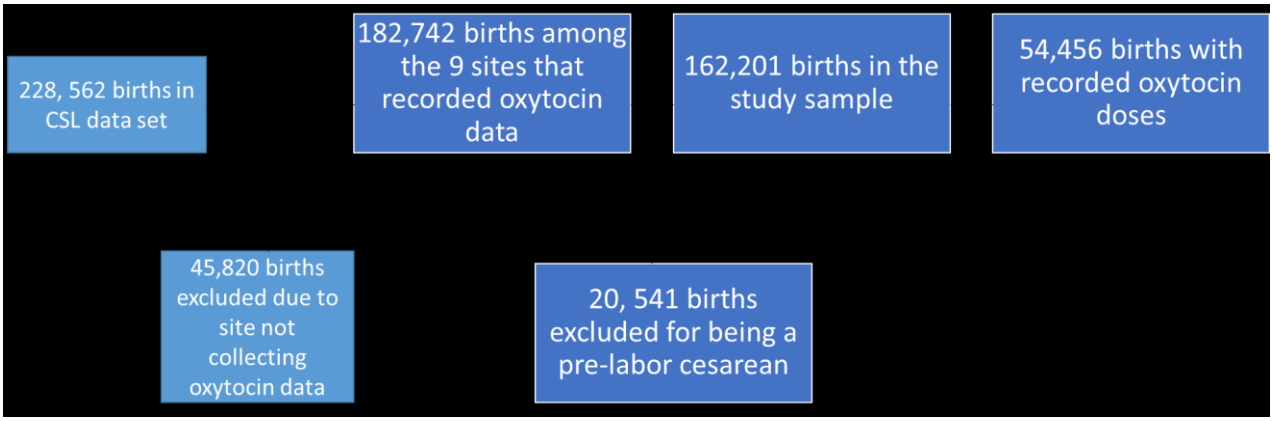
It is possible that multiple definitions of labor were used if this was not clearly defined from the beginning of the study. Another limitation was significant amounts of missing data, especially in the oxytocin data set, and the difficulty of imputing missing oxytocin data; despite this, the sample was still large when compared with similar studies[14,16], and more than met the power analysis criteria.

The original Consortium on Safe Labor (CSL) data set is large and contains a wealth of information. The data, however, was collected from 2002-2008. In 2009 the American College of Obstetricians and Gynecologists (ACOG) updated their induction of labor guidelines (reaffirmed in 2016).[124] As a result of these guidelines, elective inductions of labor prior to 39 weeks gestation have decreased in the United States, resulting in a concern that the CSL data might not reflect current usage of oxytocin usage. In the study sample, 103,617/162,201 women were missing data as to whether they received an elective induction. 15,229 women (9.4% of study sample) had elective inductions of labor; of these, 13.7% were induced prior to 39 weeks. While the number of elective inductions at less than 39 weeks may be lower today, the overall exposure to oxytocin in labor in this sample is consistent with other data from the US, Europe and Australia. Furthermore, ACOG's policy around dystocia and augmentation has not changed since 2003.[125] The recommendations around oxytocin infusion rates, provided in both the induction and augmentation policy, have not changed, either.[124,125] Therefore, despite the age of the data set, the prevalence is likely still reflective of current obstetric practice. As oxytocin infusion protocols have not changed, the age of the data set should not affect the association of oxytocin dose to postpartum hemorrhage and primary cesarean section. Prospective research specifically examining oxytocin use and its association with hemorrhage and primary cesarean is needed.

Conclusion

This is a large study using de-identified, publicly available data, to examine a significant factor in maternal morbidity and poor-quality outcomes in obstetric care. The study uses a novel approach to examine oxytocin use, as well as clinically-significant points in oxytocin exposure, to develop awareness of oxytocin over-use, offer insight into more appropriate use for the creation of policy and patient-care decisions, as well as inform future research.

Figure 3: Study Sample Flow Diagram



Oxytocin in US obstetric practice and its association with postpartum hemorrhage and primary cesarean section: A Secondary data analysis of the Consortium on Safe Labor

Introduction

Oxytocin is the hormone associated with orgasm, labor contractions, milk let-down and social bonding.[2] Oxytocin in its synthetic form is commonly used in obstetric practice to induce or augment labor, as well as prevent or treat postpartum hemorrhage (PPH). Postpartum hemorrhage is a leading cause of maternal morbidity and mortality.[3] While maternal mortality rates have decreased globally, rates of atonic PPH, the most common type of PPH, have increased in a number of high-resource countries (e.g., Australia, Canada, Ireland, US, UK).[4–11] Morbidity related to PPH is significant and may include outcomes ranging from anemia and difficulty breastfeeding to loss of fertility, postpartum depression and post-traumatic stress disorder.[12,13] Observational studies in the United States have found that patient risk factors for PPH explain little of the rise in atonic PPH.[4,5,8,10,11] Most of these studies have used the National Inpatient Sample, which provides demographic data and International Classification of Disease (ICD) codes; the ICD, however, does not contain all codes pertinent to PPH risk.[5,8,10,11] Importantly, the ICD does not contain codes for labor augmentation, or for the induction of labor with oxytocin. Oxytocin exposure in labor is an established risk factor for atonic PPH[15,16,36], as well as primary cesarean section under certain conditions, and its use in obstetric practice may be increasing.[17,18]

The reduction of primary cesarean sections is the focus of multiple quality intiatives.[19–22] Currently, 32% of births in the United States are cesarean sections.[23] These are major abdominal surgeries associated with a number of adverse outcomes including an increased risk for hemorrhage, infection, neonatal respiratory distress and complications with future

pregnancies.[24,25] Reducing primary cesareans in low-risk women is a quality indicator for the Center for Medicare and Medicaid Services' Obstetric Core Measures, as well as a Healthy People 2020 goal and an initiative for the American College of Nurse-Midwives and the American Congress of Obstetricians and Gynecologists[25–28]. Oxytocin use is an independent risk factor for cesarean sections.[19–22,29]

Background

Labor induction and augmentation can be achieved with a variety of medications and procedures, but the use of synthetic oxytocin is most common. Induction and augmentation are both independent risk factors for PPH.[8,30–32] In addition, induction or augmentation (especially in latent or early labor) of nulliparous women increases the risk of a primary cesarean section.[25] Yet, the incidence of oxytocin exposure and the dose of medication to which laboring women are exposed in not well understood, despite the fact that oxytocin could account for some of the risks associated with induction and augmentation.

Oxytocin is the drug commonly used for both induction and augmentation, and its use in labor may explain much of the increase in atonic PPH in high-resource countries.[15] Similarly, labor induction is an independent risk factor for primary cesareans, with oxytocin being the medication commonly used for induction.[19–22] Induction and augmentation rates in obstetric practice in the United States are high, but both terms cover a wide array of procedures (e.g., mechanical induction with cervical dilators to augmentation with artificial rupture of membranes to the use of oxytocin).[33–35] The incidence and character of oxytocin exposure in laboring women in hospitals in the United States is unknown. Oxytocin is a high-risk medication[1] and it is possible that its use is the main reason why induction and augmentation are independent risk factors for PPH and primary cesareans.

In order to address the high rates of PPH and primary cesareans, in order to improve the quality of obstetric care in the United States, in order to improve maternal and neonatal outcomes, oxytocin use must be better understood. To this end, the purpose of this study is to examine the use of synthetic oxytocin in obstetric practice in the US, and its association with postpartum hemorrhage and primary cesarean section, by using a nationwide sample of hospitals with inpatient obstetric units. To accomplish this purpose, the study will: 1a) examine the incidence of synthetic oxytocin exposure in women admitted for labor; 1b) to describe synthetic oxytocin exposure via "total dose" by indication, as well as patient-, provider and hospital-level variables; 2a) examine the relationship between synthetic oxytocin exposure and postpartum hemorrhage accounting for patient-, provider- and hospital-level variables; 2b) examine the relationship between amount received as measured by "total dose" and postpartum hemorrhage accounting for patient-, provider- and hospital-level variables; 2b.1) explore whether there is a clinically-relevant point of oxytocin exposure associated with the risk of PPH; 3a) examine the relationship between the receipt of synthetic oxytocin and unscheduled cesarean accounting for patient-, provider- and hospital-level variables; 3b) examine the relationship between amount received as measured by "total dose" and unscheduled cesarean accounting for patient-, provider- and hospital-level variables; and 3b.1) explore whether there is a clinically-relevant point of oxytocin exposure associated with the risk of a primary, unscheduled cesarean section. The study's a priori hypotheses were that: 1) the majority (i.e., > 50%) of hospital labors observed will include synthetic oxytocin exposure and the primary use of synthetic oxytocin will be for labor augmentation; 2) increased dose and duration of synthetic oxytocin will be associated with higher risk of PPH among women treated with this intervention, independent of patient characteristics; and 3) oxytocin exposure will be positively associated with the

occurrence of primary, unscheduled cesarean sections, while accounting for patient-level variables.

Methods

Data from the Consortium on Safe Labor data (CSL), a publicly-available database housed at the Eunice Kennedy Shriver National Institute of Child Health and Human Development, was performed to address the specific aims.[129] The CSL was initially developed to examine patterns in labor progression and the etiology of frequent cesareans in the United States.[129] Data were collected from 19 hospitals, representing the American Congress of Obstetricians and Gynecologists' nine districts, via medical chart abstraction which was coordinated by the Data Coordinating Center.[129] The database included 228,562 births between 2002-2008.[129] Patient information was de-identified before being sent to the Data Coordinating Center and is made available to researchers upon request.[129]

Study Sample

This study is a secondary data analysis of the Consortium on Safe Labor Database from the National Institute of Health. The analytic sample (see Figure 1) consisted of data from women admitted for delivery at 9 of 12 study sites that collected any oxytocin data; women were excluded from analysis if admitted for a pre-labor cesarean section. A total of 162,201 births were included in the final analytic sample; these were births at sites that collected any oxytocin data to women who had not undergone a pre-labor cesarean. A 2nd analytic sample included only study participants whose oxytocin doses administered were collected, comprised of 54,456 births and referred to as the "oxytocin sub-sample".

Measures

Oxytocin

Oxytocin exposure in the overall sample was defined as 1) entry into the oxytocin data set or 2) documented oxytocin induction or augmentation. This definition was created because not all women who received oxytocin in labor were included in the oxytocin sub-sample during data collection. The binary measure of oxytocin exposure (i.e., yes/no) was used to examine overall prevalence in the study sample.[14,93] The primary measure of oxytocin exposure was total oxytocin dose (the sum of the products of each oxytocin infusion rate multiplied by the exposure time, calculated for each individual woman, mU) and categorized by 600 mU increments up to 9600 mU after which categories increased to 1200 mU. Categorization was based on the total dose of one hour at a 10 mU/min infusion. The rationale in creating these categories was to have small increases that were clinically understandable. The secondary measure of oxytocin exposure was the maximum infusion rate (mU/min) a woman received and categorized as ≤ 10 mU/min, > 10 and ≤ 20 mU/min, > 20 and ≤ 40 mU/min and > 40 mU/min. These categories were created based on clinical relevance as most oxytocin policies have a maximum dose of 20 mU/min or, less frequently, 40 mU/min.[16,99]

Postpartum Hemorrhage

The outcomes of interest were postpartum hemorrhage (PPH) and primary cesarean section. Only early PPH was included, since hemorrhage occurring in the first 24 hours after birth is more common and more likely to be associated with an atonic uterus and, hence, oxytocin exposure. Diagnosis of postpartum hemorrhage is complicated by inaccuracies in blood loss measurement, which is typically a visual estimate. Numerous studies have found that visually estimated blood loss is inaccurate and tends towards underestimation.[138–140] Hence, postpartum hemorrhage is likely underdiagnosed. In order to improve the identification of PPH, postpartum hemorrhage diagnosis code (ICD-9) was the primary operational definition. Alternate operational

definitions of PPH, estimated blood loss (≥ 500 mL for a vaginal delivery, ≥ 1000 mL for a cesarean delivery) and postpartum transfusion, were then used to conduct sensitivity analyses.

Cesarean

Cesarean section was a binary variable based on the labor and delivery summary.

Maternal Variables

Race/ethnicity, age, gestational age, parity and body mass index were collected from the labor and delivery admission form, as well as reproductive or medical history forms. Antenatal "large for gestational age" status was collected from the participant's prenatal history. Chronic and gestational diabetes, gestational hypertension, superimposed preeclampsia, severe and moderate eclampsia and eclampsia were all derived from the participants' charts. Chronic hypertension was based on an ICD-9 code and chart data, while magnesium sulfate and fever were both collected from the labor and delivery summary. Further detail about how variables were derived was not available. All of the maternal condition variables were binary. Race/ethnicity was categorical and included the following categories: White, non-Hispanic; Black, non-Hispanic, Hispanic, Asian/Pacific-Islander, Multi-racial and Other. Age (<20, 20-34; ≥35), gestational age ($<36^0$; 36^0-37^7; 38^0-41^6; $\geq 42^0$), parity (0; 1-4; ≥5) and body mass index (<18.5; 18.5-24.9; 25-29.9; 30-34.9, 35-39.9; ≥ 40) were all categorical variables. Entry into the study was also controlled for, since some women re-entered the study with a subsequent pregnancy.

Provider and Hospital Variables

Provider type (physician, midwife, physician-midwife team) was collected from the attending provider information on the delivery note. Hospital type, either teaching university, teaching community or non-teaching community hospital, was controlled for as an independent variable.

Analysis Plan

The demographic profile of the study sample was summarized with mean and standard deviation, frequencies and percentages, or median and interquartile range, depending on the distribution of the variable. Statistical significance was set at $p \leq 0.05$.

Prevalence oxytocin exposure was examined. Exposure was presented in terms of indication (induction vs. augmentation), patient, provider and hospital characteristics. Among women who received oxytocin, exposure was described by total dose, maximum infusion rate (by category and continuous) and time in hours and reported as median and interquartile range (IQR), stratified by indication, patient characteristics and hospital type.

Multivariable logistic regression was used to examine the relationship between the receipt of oxytocin and postpartum hemorrhage accounting for patient-, provider- and hospital-level variables. Oxytocin exposure was initially measured as a binary variable, then as oxytocin total dose and maximum infusion rate category. PPH, defined by ICD-9 code, was the outcome predicted by oxytocin, age, race, parity, gestational age, body mass index, gestational diabetes, diabetes, chronic hypertension, gestational hypertension, hypertension with super-imposed pre-eclampsia, mild pre-eclampsia, severe pre-eclampsia, eclampsia, magnesium therapy[36(p56.e4)], labor dystocia, delivery mode, multiple pregnancy, macrosomia, maternal fever, entry into the study (to control for women who entered the study more than once), provider-type and hospital-type. Exploratory analyses were performed to examine if a certain amount of oxytocin exposure was associated with PPH. Predicted probabilities of PPH at different categories of oxytocin exposure were created based on the logistic regression model. As some women re-entered the study for subsequent pregnancies, a random sample was created where each woman was selected once (which entry was selected was random) and the logistic regression model was then re-run.

To further understand the effect of the sites on the associations of interest, the logistic regressions were also run stratified by site.

Multivariable logistic regression was used to examine the relationship between oxytocin exposure and primary cesarean section accounting for patient-, provider- and hospital-level variables. Oxytocin exposure was initially measured as a binary variable, then as oxytocin total dose and maximum infusion rate category. Primary cesarean was the outcome predicted by oxytocin, age, race, parity, gestational age, body mass index, gestational diabetes, diabetes, chronic hypertension, gestational hypertension, hypertension with super-imposed pre-eclampsia, mild pre-eclampsia, severe pre-eclampsia, eclampsia, magnesium therapy[36(p56.e4)], labor dystocia, multiple pregnancy, macrosomia, maternal fever, entry into the study (to control for women who entered the study more than once), provider-type and hospital-type. Exploratory analyses were conducted to examine if a certain amount of oxytocin exposure was associated with unscheduled cesarean section. Exploratory analyses will examine if a certain amount of oxytocin exposure is associated with a primary cesarean. Predicted probabilities of primary cesarean at different categories of oxytocin exposure were created based on the logistic regression model. Predicted probability of primary cesarean section with maternal race as the primary independent variable was also examined. As some women re-entered the study for subsequent pregnancies, a random sample was created where each woman was selected once (which entry was selected was random) and the logistic regression model was then re-run. To further understand the effect of the sites on the associations of interest, the logistic regressions were also run stratified by site.

Missing Data

Three sites (43, 47 and 51) from the CSL database were not included in the study sample as they did not collect oxytocin information. Sites 43 and 51 were both university teaching hospitals,

while Site 47 was a community teaching hospital. The sample size ranged from 18,392 women for Site 51 to 12,637 women for Site 43. Site 43's sample was 54.2% black and 30% Hispanic while Sites 47 and 51 were 58% and 55.3% white, respectively. Combined, these three sites had 45,695 women with a mean parity of 0.97 and mean gestational age of 38.6 weeks. Women from these three sites ranged in age from 12-58 with a mean age of 29.1 years and had a mean BMI of 25.3 kg/m^2. Most of the women from these sites were missing data on education level, but 60.8% of the women were married and 42.9% had private insurance (30.8% had public insurance). There were more black and Hispanic women in the sample from the three sites than in the study sample. Compared to the study sample, women from the three sites had a lower mean parity and a higher mean age.

20,541 women were excluded from the study sample due to having a pre-labor cesarean section. These women were more likely to be black (28.4%) or Hispanic (21.1%) compared to the overall study sample. Mean parity for the women with a pre-labor cesarean was 1.36 and the mean gestational age was 37.3 weeks. Mean age and mean BMI were 29.8 and 27.8 kg/m^2, respectively, which is both older and heaver than the overall study sample.

In the study sample, oxytocin dose data were only collected for some of the women. Demographic data was examined to understand some of the overall differences between the women in the oxytocin dose sub-sample and the women for women no oxytocin dose data was collected. Women in the study sample, but not the oxytocin dose sub-sample, were 48.5% white, 21.1% black and 17.5% Hispanic with a mean age of 27.2 years and a mean BMI of 25.1 kg/m^2. They had a mean parity of 1.2 children and a mean gestational age of 38.5 weeks. The most remarkable difference between the two groups of women was the difference in racial/ethnic make-up of the groups (61.5% white in the oxytocin dose group vs. 48.5% white in the no

oxytocin dose group), though the other demographic categories were statistically significantly different.

1,374 (2.5%) women were dropped from the oxytocin-PPH model due to missing data. This missing data were predominantly missing BMI (734), following by a missing oxytocin dose category (543), with 34 women missing provider-type and 8 missing age. 1,295 (2.4%) women were dropped from the oxytocin-primary cesarean model due to missing data. This missing data were predominantly missing BMI (734), oxytocin dose category (543) and age (8).

Results

Sample Demographics

The study sample consisted of 162,201 women (some of whom reentered the study with subsequent pregnancies). The sample was 52.8% white, 20.1% black and 16.3% Hispanic with a mean parity of 1.16, mean age of 27.25 years, mean BMI of 25.3 kg/m^2 and a mean gestational age of 38.6 weeks. 41.1% of the study population was nulliparous, while 55.9% had 1-4 children. 77.7% of the women in the study ranged in age from 20-34. The BMIs of women in the study were concentrated in the normal range of 18.5-24.9 kg/m^2 and in the obese category of ≥ 40 kg/m^2 at 35.3% and 36.7%, respectively. 52.5% of women in the study had a gestational age of 39-40.6 weeks, followed by 27.9% of women between 37-38.6 weeks. For a more detailed description of the sample demographics, please see Table 5.

Specific Aim 1

The first specific aim was to examine the incidence of synthetic oxytocin exposure in women admitted for labor and then, in the oxytocin subset, to describe synthetic oxytocin exposure via "total dose" by indication, as well as patient-, provider and hospital-level variables. The sample included 162,201 births from nine different hospitals. Of these, 106,958 (65.9%) were exposed to

oxytocin. 31,614 (19.5%) women were marked as being induced with oxytocin, while 54,654 women (33.7%) were marked as being augmented with oxytocin. Oxytocin dosing data was available for 54,456 women in the study sample. 19.6% of the 162,201 births ended in a cesarean section, 73.1% of which were primary cesarean sections.

Due to variation in the data collected at different sites, the nine sites which had collected any oxytocin data were included in the sample. Of the nine sites, only five sites (41, 42, 44, 46 and 52) collected specific oxytocin doses. Sites 42, 44 and 49 were predominantly Black-serving (see Appendix 1); Sites 41, 45, 46, 50 and 52 were predominantly White serving and Site 48 was predominantly Hispanic serving (53.4% Hispanic; 29.5% Black). All sites, except 50, reported a greater than 50% oxytocin exposure rate; Site 50 (67.4% White, 13.6% Asian/PI) reported at 48% oxytocin exposure rate. The two sites with the greatest exposure rates were 44 and 48 at 99.96 and 89%, respectively. In terms of predominantly white-serving hospitals, three of them reported that less than 10% of patients were black; sites 46 and 52 reported a patient population 32.5 and 25.4% black, respectively.

Overall, the probability of being exposed to oxytocin during labor in the overall sample, while controlling for age, parity, gestational age, body mass index, site and study entry was 65.9% (SD 17.2%). The sample for this model may be seen in Figure 5. When the model was expanded to control for maternal conditions (chronic diabetes, gestational diabetes, chronic hypertension, gestational hypertension, preeclampsia superimposed on chronic hypertension, mild preeclampsia, severe preeclampsia, eclampsia, magnesium sulfate exposure, macrosomia and intrapartum fever), provider and hospital type, site, entry, race and labor length, the predicted probability of being exposed to oxytocin was 65.98% (SD 18.5%).

The oxytocin subset was used to describe synthetic oxytocin exposure via "total dose" by indication, as well as patient-, provider and hospital-level variable. Total dose ranged from 1 – 108,000,000 mU; 860 mU was the 25th percentile, 2618 mU was the 50th percentile, 5936 mU was the 75th percentile, 15,114 mU was the 95th percentile and 26,977 mU marked the 99th percentile (see Table 9). Total time of oxytocin exposure ranged from 0.02 to 943,841 hours; 3.8, 6.1, 9.4, 17.2 and 29.7 hours marked the 25th, 50th, 75th, 95th and 99th percentiles, respectively. The maximum oxytocin infusion rate ranged from 1-1200 mU/min; 7, 12, 20, 30 and 40 mU/min marked the 25th, 50th, 75th, 95th and 99th percentiles, respectively. Figure 1 describes the exposure of total oxytocin dose in greater detail; 20.3% of births were exposed to 0-600 mU of oxytocin, 10.9% of births were exposed to 600-1200 mU of oxytocin and 4.1% of births were exposed to 15,000-27,000 mU of oxytocin. From a different perspective, 44.1% of births involved a maximum oxytocin infusion rate of ≤ 10 mU/min, 42.3% of births involved a maximum oxytocin infusion rate of between 10-≤20 mU/min, 13.4% of births were exposed to an oxytocin infusion rate of 20-≤40 mU/min and 0.2% (115) births were exposed to an oxytocin infusion rate > 40 mU/min.

Oxytocin exposure increased after 41 weeks gestational age and with body mass index > 25 kg/m^2 (though it decreased slightly for body mass index > 40 kg/m^2); oxytocin exposure decreased with increasing parity and maternal age. Oxytocin exposure was increased for Black and Hispanic women, compared to White, non-Hispanic women (see Table 10). Significant data was missing for the indication for oxytocin exposure (induction or augmentation); 20.6% of the women in the study sample were marked as being augmented with oxytocin, but 61% of women are missing data on whether they received augmentation. 37.2% of women in the study were induced, 19.5% of women were induced with oxytocin specifically and, of these, 9.1% were

augmented with oxytocin as well. The probability of oxytocin exposure is decreased when the birth attendant is a midwife (59.8%) compared to a physician (67.9%), controlling for all other variables. Oxytocin exposure was less likely at a University-affiliated teaching hospital (59.2%) compared to a teaching community hospital (68%) but was similar to the 59.4% probability of oxytocin exposure at a non-teaching community hospital. Despite the pattern in the raw numbers, when controlling for confounders, the probability of oxytocin exposure was greatest for Asian/PI women (71.2%), followed by White, non-Hispanic women (66.7%) and then Black, non-Hispanic and Hispanic women (64.1 and 64.2%, respectively). The reason for this change is controlling for the Site, suggesting that the delivery site plays an integral role in oxytocin exposure. These findings are similar to those reported by Nippita et al.[141] regarding the role of provider and hospital culture in induction. This finding also agrees with other studies which have found that the hospital itself plays a critical role in racial differences noted in labor management and outcomes.[142–144] Similar to the pattern seen in the raw numbers, the probability of oxytocin exposure increases with body mass index > 25 kg/m^2 but decreases with a body mass index > 40 kg/m^2.

Specific Aim 2

The second specific aim examined the relationship between oxytocin exposure and postpartum hemorrhage accounting for patient-, provider- and hospital-level variables in the study sample. Then, using the oxytocin subset, the relationship between "total dose" and postpartum hemorrhage was examined accounting for patient-, provider- and hospital-level variables and the data was examined for points in exposure where risk of hemorrhage increased significantly. The probability of postpartum hemorrhage was 2.9% in the study sample, controlling for confounders. In raw numbers, the incidence of postpartum hemorrhage (ICD-9) was also 2.9%.

Any oxytocin exposure (as compared to none) increased the odds of a postpartum hemorrhage (ICD-9) by 1.2 (1.09-1.31). In the oxytocin subset, the incidence of postpartum hemorrhage (ICD-9) is 3.21%. Figure 6 presents the sample for the oxytocin-postpartum hemorrhage regression. Variables controlled for in the model included maternal characteristics (age, parity, gestational age, body mass index and race), maternal conditions (chronic diabetes, gestational diabetes, chronic hypertension, gestational hypertension, preeclampsia superimposed on chronic hypertension, mild preeclampsia, severe preeclampsia, eclampsia, magnesium sulfate exposure, macrosomia and intrapartum fever), provider and hospital type, study entry, labor length and mode of delivery. Hispanic (37% increase compared to white) or Asian/Pacific Islander (34% compared to white) race/ethnicity statistically significantly increased the odds of a PPH.

When examining categories of oxytocin total dose (mU), 6000 mU (roughly equivalent to receiving a 20 mU/min infusion of oxytocin for less than 5 hours) was the first point where the probability of postpartum hemorrhage was statistically significantly greater than the probability of PPH with no oxytocin exposure, all other variables held constant (see Figure 8). After running several different models, the decision was made to keep 6000 mU and 15000 mU as statistically, and potentially, clinically, significant points of oxytocin exposure (see Figure 9). With these "cut points", the model reported a statistically significant 75% increase in the odds of PPH (ICD-9) at 6000-15000 mU of oxytocin exposure, compared to less than 6000 mU of exposure and a 148% increase in the odds of PPH (ICD-9) with an oxytocin exposure of 15000-27000 mU, all other variables being held constant (sample 51,372). The probability of having a PPH (ICD-9) increased from 2.6% in those receiving less than 6000 mU of oxytocin (compared to 2.9% in the overall population) to 4.5% in the 6000-15000 mU category and 6.1% in the 15000-27000 mU category, all of which were statistically significant and statistically significantly different from

each other (see Figure 4). There were 41,021 births exposed to ≤ 6000 mU of oxytocin, 10,673 exposed to 6000-15,000 mU and 2,219 exposed to 15000-27000 mU.

This model was then re-run, stratifying by parity. The probability of postpartum hemorrhage for nulliparous women increased from 2.8% (2.5-3% 95% CI) to 5.2% (4.6-5.8%) to 6.8% (5.5-8.1%) for 0-6,000, 6,000-15,000 and 15,000-27,000 mU of oxytocin exposure, respectively. Multiparous women with 1-4 children had a probability of postpartum hemorrhage that increased from 2.4% (2.2-2.6%) to 3.5% (3-4.1%) to 5.4% (3.5-7.3%) for the same three categories of oxytocin exposure. Multiparous women with greater than or equal to 5 children had the greatest probability of postpartum hemorrhage, starting with a probability of 4.6% (3.3-5.9%) at 0-6000 mU, then increasing to 6.6% (2.2-10.95%) at 6,000-15,000 mU and 16% (1.9-30.2%) at 15,000-27,000 mU. All of these probabilities were statistically significant.

When the model was re-run using a random sample (for women who entered the study more than once, one of the entries was randomly selected), the probability of postpartum hemorrhage went from 2.6% (2.5-2.8% 95% CI) at 0-6,000 mU to 4.3% (3.9-4.7%) at 6,000-15,000 mU to 6.3% (5.3-7.3%) at 15,000-27,000 mU. This same random sample was then used to run the model stratified by site (see Table 8), which shows the shift in the odds of postpartum hemorrhage by oxytocin total dose category by site, controlling for the other variables in the model.

The second model conceptualized oxytocin exposure by infusion categories. Compared to having a maximum oxytocin infusion rate of ≤ 10 mU/min (24,011 births), every other category statistically significantly increased the odds of a PPH (ICD-9), all other variables held constant (see Figure 10). Receiving a maximum infusion of ≤ 20 mU/min (23,010 births) increased the odds by 45%, ≤ 40 mU/min (7,320 births) by 116% and > 40 mU/min by 451% (only 115

women in the sample, however, received an oxytocin infusion > 40 mU/min). The probability of having a PPH (ICD-9), given a maximum infusion ≤ 10 mU/min was 2.6% (compared to 2.9% in the overall study sample), it increased to 3.7%, 5.4% and 12.3% in the ≤ 20 mU/min, ≤ 40 mU/min and > 40 mU/min groups, respectively, all other variables being held constant.

Two different sensitivity analyses were run to identify whether incidence of postpartum hemorrhage had been well-captured. Postpartum hemorrhage was defined first by estimated blood loss and, secondly, by postpartum transfusion. In the sample, most blood transfusions were received by women who were recorded as losing less than 500 mL of blood after giving birth, which suggests something of the difficulty of determining the true incidence of postpartum hemorrhage. 19,527 of 54,456 births were missing estimated blood loss information. 27,825 births involved < 500 mL blood loss, 5,966 births 500-1000 mL, 898 births 1000-1500 mL and 240 births > 1500 mL. As oxytocin exposure increased, the probability of remaining in the < 500 mL blood loss group decreased, and, for the other three categories, the probability of being in that category increased with oxytocin exposure in a statistically significant manner (see Figure 11). For example, the probability of losing 500-1000 mL of blood, all other variables held constant, is 16% if oxytocin exposure is less than 6000 mU, increases to 18.3% with 6000-15000 mU and then to 19.4% with 15000-27000 mU. Again, the probability of losing 1000-1500 mL of blood, all other variables held constant, is 2% if oxytocin exposure is less than 6000 mU but increases to 2.8% is exposure is 6000-15000 mU and increases again to 3.2% if exposure is 15000-27000 mU. Estimated blood loss, typically a visual measure, is well-documented as underestimating actual blood loss. This sensitivity analysis supports the association of increased blood loss with increased oxytocin exposure.

The same pattern may be seen with maximum oxytocin infusion (mU/min) as the independent variable of interest (see Figure 12). All other variables held constant, as the maximum oxytocin infusion rate increases, the probability of inclusion in the < 500 mL blood loss group decreases and the probability of inclusion in any of the three other groups increases. For example, the probability of losing 500-1000 mL, if one's maximum infusion rate is ≤ 10 mU/min is 16%, increasing to 17.1%, 19% and 22.9% for maximum rates of 20, 40 and > 40 mU/min, respectively.

The total dose of oxytocin exposure (mU) does not statistically significantly increase the odds of postpartum transfusion. Receiving a maximum oxytocin infusion rate of > 20 mU/min and ≤ 40 mU/min (6,344 births), compared to a rate of ≤ 10 mU/min, does statistically significantly increase the odds of a postpartum blood transfusion, all other variables held constant, by 21%. The probability of receiving a transfusion increases from 6.1% to 7.3%.

Specific Aim 3

The third specific aim examined the relationship between the receipt of oxytocin and unscheduled cesarean accounting for patient-, provider- and hospital-level variables. Then the relationship between amount received as measured by "total dose" and unscheduled cesarean was examined using the oxytocin subset, accounting for patient-, provider- and hospital-level variables. The oxytocin subset was explored to discover whether there was a clinically-relevant point of oxytocin exposure associated with the risk of a primary, unscheduled cesarean section.

In the overall sample model (80,304 births), controlling for confounders, the probability of a primary cesarean is 11.8%. In the entire sample of 162,201 births, 14.3% of births ended in a primary cesarean (overall cesarean rate of 19.6%, significantly below the national average). From a different perspective, 72.9% of primary cesareans were preceded by oxytocin exposure;

67.4% of vaginal births (not including vaginal birth after cesarean or assisted deliveries) were preceded by oxytocin exposure. In the oxytocin subset, 12.9% ended in primary cesarean and 0.6% were repeat cesareans. Figure 7 presents the primary cesarean model sample. Any oxytocin exposure increases the odds of a primary cesarean section by 71.4%, compared to no oxytocin exposure, all other variables being held constant. Due to the common nature of cesarean sections, the odds ratio does not approximate the risk well. Variables controlled for in the model included maternal characteristics (age, parity, gestational age, body mass index and race), maternal conditions (chronic diabetes, gestational diabetes, chronic hypertension, gestational hypertension, preeclampsia superimposed on chronic hypertension, mild preeclampsia, severe preeclampsia, eclampsia, magnesium sulfate exposure, macrosomia and intrapartum fever), provider and hospital type, study entry and labor length. Black (compared to white) race/ethnicity statistically significantly increased the odds (by 39.6%) of having a primary cesarean.

In determining doses of oxytocin exposure that statistically significantly increased the probability of primary cesarean section the "mchange" table was examined. Figure 10 shows the margin plot displaying probability of primary cesarean section given changing category of oxytocin total dose exposure. A small, though statistically significant, decrease in primary cesarean section was noted with total doses varying from 600-3600 mU, compared to less than 600 mU (see Figure 13). After this, the probability of primary cesarean increased with total oxytocin dose; increased probability was noted particularly at 4200, 7800 and 12,000 mU (see Figure 14). 4200 mU is equivalent to three and a half hours on an oxytocin infusion of 20 mU/min; at the same infusion rate, 7800 mU is six and half hours and 12000 mU is ten hours. Due to titration, women would reach the 4,200-mU mark sooner than three and a half hours.

These three exposure points are statistically significantly different from each other and from zero ($p = 0.000$). With an oxytocin exposure ranging from 0-4200 mU, the probability of a primary cesarean section is 10.7%. The probability of a primary cesarean with an oxytocin total dose ranging from 4200-7800 mU, 7800-12000 mU and 12,000-27,000 mU is 12.7, 16.7 and 21.7%, respectively (all statistically significant), all other variables held constant and based on a sample of 51,026[2] births.

This model was then re-run, stratifying by parity. The probability of a primary cesarean for nulliparous women increased from 19.3% to 23.4% to 28.9% to 34.8% for 0-4,200, 4,200-7,800, 7,800-12,000 and 12,000 to 27,000 mU of oxytocin exposure, respectively. Multiparous women with 1-4 children had a probability of primary cesarean section that increased from 4.1% to 4.1% to 6.6% to 10.5% for the same four categories of oxytocin exposure. Multiparous women with greater than or equal to 5 children had a probability of primary cesarean section that started with a probability of 3.8% at 0-4,200 mU, increasing to 4.6% at 4,200-7,800 mU, 8% at 7,800-12,000 mU and 16.1% at 12,000-27,000 mU. All of these probabilities were statistically significant.

When the model was re-run using a random sample (for women who entered the study more than once, one of the entries was randomly selected), the probability of primary cesarean went from 10.96% (10.61-11.3% 95% CI) at 0-4,200 mU to 13.1% (12.45-13.8%) at 4,200-7,800 mU to 17.62% (16.65-18.59%) at 7,800-12,000 mU to 22.55% (21.4-23.69%) at 12,000-27,000 mU. This same random sample was then used to run the model stratified by site (see Table 9),

[2] For the three primary cesarean models, the oxytocin subset of 54,456 births was the sample. Differences in the births included in each model are due to births being dropped by the model due to missing data.

which shows the shift in the odds of primary cesarean section by oxytocin total dose category by site, controlling for the other variables in the model.

In the second primary cesarean model (51,455 births), oxytocin was conceptualized as the maximum infusion rate (mU/min). A maximum infusion rate of ≤ 10 mU/min was not statistically significantly different compared to >10 - ≤ 20 mU/min with regards to the prediction of the probability of a cesarean, so the two groups were combined. The probability of a primary cesarean, all other variables held constant, was 11.6% for births in the ≤ 20 mU/min group and 20.3% in the > 20 mU/min group.

While not an initial aspect of the study aims, the difference between racial/ethnic groups with regards to the probability of a primary cesarean, especially for black women, was striking (see Figure 15). The sample size was 51,026 births. The probability of a primary cesarean section, all other variables in the model held constant, was 11.4% for white women, 13.77% for Asian/Pacific-Islander women, 13.97% for Hispanic women and 16.1% for Black women. There were only 1,502 Asian/Pacific-Islander women in the sample; the probability of primary cesarean section for each racial/ethnic group was statistically significantly different from each other, except Hispanic and Asian/Pacific-Islander women.

The model was then re-run with an interaction term for the relationship between race/ethnicity and oxytocin dose category. When oxytocin total dose ranged from 0-4200 mU during labor, white women had a 9.69% probability of a primary cesarean section while black women had a 15.9% probability. Exposure to 4200-7800 mU of oxytocin increased the probability of a primary cesarean to 11.97% while the probability for black women remained that same at 15.9%. From 7800-12000 mU of oxytocin exposure, white women had a 16.2% and black women had a 19.66% probability of a primary cesarean section. Finally, an oxytocin total

dose from 12,000-27,000 mU was associated with a 21.19% and a 25.07% probability of a primary cesarean section for white and black women, respectively.

Discussion

This study is unique in specifically purposing to characterize the use of oxytocin in labor in the United States. It also significantly advanced the measurement of one of the most common, and powerful, medications used in labor. It is one of a few studies to examine oxytocin exposure as a continuous variable. It is unique in its pharmacoepidemiologic approach to examining oxytocin use, and oxytocin's dose-specific association with primary cesarean section. At least two other studies examine oxytocin dosing in relation to the outcome of postpartum hemorrhage.[14,16] This study is unique in examining the data for clinically relevant points of oxytocin exposure as suggested by small increments in total dose. Specifically, this study found that the probability of any oxytocin exposure in this sample was 65.9%. Receiving a total dose of oxytocin greater than 6000 mU or 4200 mU statistically significantly increased the risk for a postpartum hemorrhage or primary cesarean, respectively. Furthermore, having a maximum infusion rate ≥ 10 mU/hr significantly increased the risk for a postpartum hemorrhage, while a maximum infusion ≥ 20 mU/hr significantly increased the risk of a primary cesarean.

Oxytocin exposure is typically measured as a binary variable, even though it's a continuous exposure. In order to refine the measurement of oxytocin exposure, two studies conducted in 2011 introduced continuous measurement of oxytocin exposure via "total dose"[16] or "area under the curve"[36]. As a continuous measurement, total dose is difficult to interpret, so both studies created a categorical variable based on total dose. Belghiti et al[50]. used the 50th, 75th and 90th percentiles to create total dose categories; Grotegut et al.[36] examined total dose in 5000 mU increments. Grotegut et al. noted that they believed that categories in 5000 mU increment

would have more significant clinical implications than 1 mU increments or creating a binary variable based on total dose.[36(p56.e5)] In addition to total dose, Belghiti et al.[50] examined oxytocin as a binary variable and in terms of maximum infusion rate (mU/min) and total duration of exposure (min). In 2015, three studies used different methods to measure oxytocin exposure: total dose (mU)[92], maximum infusion rate (mU/min)[93] and a comparison of maximum infusion rate at greater or less than and equal to 20 mU/min[94]. Both studies[93,94] that looked at rate did so in order to gather information to improve oxytocin protocols; none gave specific rationale behind the measurement method chosen. Two 2017 studies used a variety of methods for measuring oxytocin exposure: mean and maximum oxytocin infusion rate (mU/min), hourly and total oxytocin dose (IU and mU)[95] and the duration of each specific infusion rate as well as total duration (min) of oxytocin exposure (min)[96]. In 2018, two studies[97,98] used a variety of methods to measure oxytocin exposure. One study examined initial, average and maximum infusion rate, as well as duration, to examine the impact of instituting an oxytocin checklist on usage and outcomes.[97] The other study used maximum oxytocin rate (mU/min), total duration (h), oxytocin product (mU/min*h [sic]) and total dose (mU) in order to determine whether the product of maximum rate times total duration would be a good surrogate for total dose.[98(p79)] The present study has advanced the science by examining small intervals of oxytocin total dose and providing a rationale so that future studies may expand upon it.

While controlling for maternal conditions and characteristics, provider and hospital type, site, entry and labor length, the predicted probability of oxytocin exposure during labor was 65.98% (SD 18.5%), based on a sample of 159,394 births. Median total dose in the sample was 2618 mU while 5936 mU marked the 75th percentile and 15,114 mU marked the 95th. A total dose of 2618 mU equates to roughly a 20 mU/min infusion for two hours. The median total time

of exposure was 6.1 hours, with 9.4 and 17.2 hours marking the 75th and 95th percentiles, respectively. Both total dose and total time of oxytocin exposure had an exceedingly wide range. Maximum oxytocin infusion rate had a median of 12 mU/min; 30 and 40 mU/min marked the 75th and 95th percentiles.

Oxytocin exposure is an independent risk factor for postpartum hemorrhage, accounting for patient, provider, hospital-level variables. This study advanced the science by examining the oxytocin dose and its association with postpartum hemorrhage. The probability of a postpartum hemorrhage in the study sample was 2.9% which decreased slightly to 2.6% among women who received less than 6000 mU of oxytocin and then increased to 4.5% in women who received 6000-15000 mU and 6.1% in women who received 15000-27000 mU. The 6000 mU exposure point is not so different from the 5000 mU point identified by Grotegut et al.[14] The probability of postpartum hemorrhage increased significantly with each maximum infusion rate over 10 mU/min. These findings corroborate two other studies which found that maximum infusion rates > 10 mU/min[16] and > 20 mU/min[14] increased the odds of postpartum hemorrhage secondary to uterine atony.

Oxytocin exposure as a risk factor for postpartum hemorrhage has been demonstrated in other studies. These studies, however, frequently operationalize exposure as a binary variable or use "induction" or "augmentation", variables which include a range of medications and procedures. A few studies have conceptualized oxytocin exposure in labor as "total dose" or "maximum infusion rate" while examining the outcome of postpartum hemorrhage.[14,16,99] In the two studies which used total dose, categories of oxytocin exposure were created at 5000 mU increments[14] or by percentiles present in the data[16]; while both studies found increased oxytocin exposure increased the odds of a postpartum hemorrhage, the categories were large or based on a

specific data set, thereby making comparisons from future studies difficult. Smaller categories based on clinical utility were used in this study to better understand when, in terms of dose and time, the probability of a postpartum hemorrhage due to oxytocin exposure increased significantly. The probability of a postpartum hemorrhage in the study sample was 2.9% which decreased slightly to 2.6% among women who received less than 6000 mU of oxytocin and then increased to 4.5% in women who received 6000-15000 mU and 6.1% in women who received 15000-27000 mU. The 6000 mU exposure point is not so different from the 5000 mU point identified by Grotegut et al.[14] The probability of postpartum hemorrhage increased significantly with each maximum infusion rate over 10 mU/min. These findings corroborate two other studies which found that maximum infusion rates > 10 mU/min[16] and > 20 mU/min[14] increased the odds of postpartum hemorrhage secondary to uterine atony.

In the oxytocin subset of the study sample, the probability of a primary cesarean section increased significantly beyond a 4200-mU oxytocin exposure (roughly equivalent to 3.5 hours on a 20 mU/min infusion). The probability of a primary cesarean section, all other variables held constant, started at 10.7% for women exposed to less than 4200 mU of oxytocin and increased to 12.7, 16.7 and 21.7% at 4200, 7800 and 12000 mU, respectively. The probability of a primary cesarean, all other variables held constant, was 11.6% for births in the ≤ 20 mU/min group and 20.3% in the > 20 mU/min group. Exposure to any oxytocin, all other variables being held the same, increases the probability of having a primary cesarean section significantly, though only by 1.2% (overall, the probability of having a primary cesarean given any oxytocin exposure is 15.5%, compared to a 14.3% probability with no oxytocin exposure). It is possible that this different would have been greater if the cesarean section rate in the study sample was closer to the national average. Zhang et al.[45] reported an overall cesarean rate of 30.5% in the full

Consortium on Safe Labor data and noted that half of the cesareans for dystocia were performed before 6 cm dilation (i.e., before active labor).

Prior to this study, an examination of oxytocin's dose-association with primary cesarean section was not available in the literature. Race/ethnicity was also found to significantly influence the probability of having a primary cesarean, all other variables held constant. Compared to White women, for whom the probability of a primary cesarean was 11.4%, the probability of a primary cesarean for Black women was 16.1%, while for Asian/PI and Hispanic women, the probability was 13.77 and 13.97%, respectively. These findings agree with those of a number of other researchers who have found that Black women are disproportionately more likely to receive a primary cesarean section.[145–149] Black women in this sample were more likely to receive a cesarean section for non-reassuring fetal tones; these findings agree with several other studies.[146,147,149]

Several recommendations are suggested by this research and related studies. Tracking the total oxytocin dose a woman has received may improve both health care team communication, clinical decision-making and risk assessment for the laboring woman. Specifically, awareness of the total dose received may help providers better understand the increasing nature of the risk the women in their care are being exposed to – and to discuss those risks with women and mitigate them to the best of their ability. This might be especially useful where multiple providers care for a woman over a number of shifts to improve communication and decision-making. Providers might also consider discussing the increased probability of hemorrhage and primary cesarean section as part of their informed consent discussion around oxytocin. Further, providers in charge of practice protocols might also reconsider oxytocin infusion protocols that go beyond 20 mU/min. Other studies have examined checklists[97,111,112], partograms[150] and interventions such as

stopping oxytocin once a woman is in active labor[113,151], as means to reduce oxytocin use and primary cesarean section with encouraging outcomes. In the national effort to reduce primary cesarean sections, we might do well to pay attention to decreasing unnecessary primary cesarean sections for Black women. Further research is needed to better understand why Black women are more likely to undergo cesarean section for non-reassuring fetal heart tone.

Strengths

This study has numerous strengths. The sample was a large one drawn from sites around the country. This is the first study to specifically examine the prevalence and characteristics of oxytocin use in hospitals from different parts of the country. The sample population was large enough to meet the study's specific aims of examining the dose-association of oxytocin with postpartum hemorrhage and primary cesarean section. This study also used smaller categories of oxytocin total dose in order to gain a more finally detailed understanding of the drug's association with the outcomes of interest. While using more finally delineated categories of oxytocin total dose, this research also corroborates other research conducted in the US[36,93] and France[16] regarding oxytocin's dose-association with postpartum hemorrhage. This study also examined the association of oxytocin dose with primary cesarean section, which has not been presented in the literature previously. Finally, this study corroborates the findings of other researchers that there are racial disparities in the primary cesarean section rate, with black women more likely to undergo the procedure – and to undergo it for non-reassuring fetal heart tones – than white women.[145,146,152]

Limitations

The study faced a number of limitations. This was a secondary data analysis, so the original data was not collected to address this study's specific research questions. Due to the nature of the

study, it was difficult to address problematic missing data and variable definitions were not always clear all of which increased the probability of different kinds of bias. Bias was addressed, in part, by having a data analysis plan prior to beginning the study, triangulating variable definitions where possible and running sensitivity analyses. One variable that posed difficulty was pre-labor cesarean (n=20,541), which, ostensibly, identified women who had a pre-labor cesarean delivery. These women were to be excluded from the study, per the analysis plan, as they would not be at-risk for intrapartum oxytocin exposure. Upon examining the raw data, however, some of the women marked as having a pre-labor cesarean also appeared to have labored. This difficulty was addressed by also excluding these women from the study, in order to remain consistent with the original study's coding. If anything, this would make the probabilities reported in this study more conservative. The three sociodemographic variables collected for the study (education, insurance and marital status) had a lot of missing data. While some research has included sociodemographic variables in models examining maternal outcomes, one recent nation-wide study found that race/ethnicity was the most important factor, and this variable was included in the models.[153]

The original Consortium on Safe Labor sample was chosen and weighted to be representative of the US as a whole[45(p326.e10)]. For this study, a different study sample was created from the original one and is not necessarily representative. For instance, the cesarean section rate is far lower in this study sample than in the original (and in the US as a whole) and the racial/ethnic make-up of the study sample also varies somewhat. The indication for oxytocin augmentation was missing for a significant portion of the study population, limiting what can be understood from the study about rationale for oxytocin use in labor. Further, no variables were collected by the original study to capture communication or clinical decision-making which are

critical components of oxytocin use. While care should be taken, then, in generalizing the results of this study, it is still a large sample drawn from sites around the country and offers insight into oxytocin use. Further research, especially prospective studies that are generalizable to the wider US population, account for indication for oxytocin use, timing of administration (i.e., in active versus latent labor), and clinical decision-making around oxytocin use will help further clarify how oxytocin is being used and its effects on maternal and neonatal outcomes and satisfaction with care. Despite the shift in sample make-up, the sample population was sufficient to examine the study's specific aims regarding the nature of oxytocin use and its association with postpartum hemorrhage and primary cesarean section.

Conclusion

Oxytocin is a life-saving, but high-alert, medication used in more than half of the labors in the United States. If practice in other high-income countries is similar to US practice, it is likely that oxytocin is frequently used without a medical indication, especially for labor augmentation. Specific oxytocin total doses and infusion rates are associated with a greater risk of postpartum hemorrhage and primary cesarean section. The way oxytocin is currently used in US obstetrics is tied to many factors, patient, provider and hospital. It will take a culture-change in obstetrical care to shift how we use oxytocin, but such change is possible. Oxytocin use is tied to maternal morbidity and quality outcomes, but its use, while frequent in other high-resource countries, is not associated with the same degree of adverse maternal and neonatal outcomes as we see here in the US. Oxytocin is just a piece in a much larger jigsaw puzzle, but a critical piece and one amenable to intervention to improve outcomes.

Variable	$n_{9\ sites}$ (%) 162,201	$n_{3\ sites}$ (%) 45,695	$n_{pre\text{-}labor\ cesarean}$ (%) 20,541	$n_{sample,\ no\ oxy\ dose}$ (%) 107,744	$n_{oxytocin}$ (%) 54,457
Race					
White	85,702 (52.8)	19,646 (43)	7,876 (38.3)	52,240 (48.5)	33,462 (61.5)
Black	32,664 (20.1)	12,888 (28.2)	5,840 (28.4)	22,737 (21.1)	9,927 (18.2)
Hispanic	26,432 (16.3)	8,956 (19.6)	4,328 (21.1)	18,876 (17.5)	7,556 (13.9)
Asian/PI	5,848 (3.6)	2,707 (5.9)	790 (3.9)	4,347 (4)	1,501 (2.8)
Parity Mean (SD)	1.16 (1.4)	0.97 (1.2)	1.36 (1.2)	1.2 (1.6)	1.09 (1.3)
Age Range	11-55	12-58	12-55	12-55	11-48
Age Mean (SD)	27.25 (6.06)	29.1 (6.5)	29.8 (6.3)	27.2 (6.1)	26.5 (5.59)
BMI Mean (SD)	25.3 (1.4)	25.3 (6.4)	27.8 (7.4)	25.1 (6)	25.4 (6.1)
Gestational Age Mean (SD)	38.6 (2.3)	38.6 (2.49)	37.3 (3.2)	38.5 (2.5)	38.8 (1.8)
Insurance Status					
Private	97,257 (59.96)	19,579 (42.9)	11,197 (54.5)	64,741 (60.1)	32,516 (59.7)
Public	50,835 (31.3)	14,074 (30.8)	8,731 (42.5)	30,210 (28)	20,625 (37.9)

Table 5: Demographics

Variable	$n_{9\ sites}$ (%) 162,201	$n_{3\ sites}$ (%) 45,695	$n_{pre\text{-}labor\ cesarean}$ (%) 20,541	$n_{sample,\ no\ oxy\ dose}$ (%) 107,744	$n_{oxytocin}$ (%) 54,456
Race					
White	85,702 (52.8)	19,646 (43)	7,876 (38.3)	52,240 (48.5)	33,462 (61.5)
Black	32,664 (20.1)	12,888 (28.2)	5,840 (28.4)	22,737 (21.1)	9,927 (18.2)
Hispanic	26,432 (16.3)	8,956 (19.6)	4,328 (21.1)	18,876 (17.5)	7,556 (13.9)
Asian/PI	5,848 (3.6)	2,707 (5.9)	790 (3.9)	4,347 (4)	1,501 (2.8)
Parity Mean (SD)	1.16 (1.4)	0.97 (1.2)	1.36 (1.2)	1.2 (1.6)	1.09 (1.3)
Age Range	11-55	12-58	12-55	12-55	11-48
Age Mean (SD)	27.25 (6.06)	29.1 (6.5)	29.8 (6.3)	27.2 (6.1)	26.5 (5.59)
BMI Mean (SD)	25.3 (1.4)	25.3 (6.4)	27.8 (7.4)	25.1 (6)	25.4 (6.1)
Gestational Age Mean (SD)	38.6 (2.3)	38.6 (2.49)	37.3 (3.2)	38.5 (2.5)	38.8 (1.8)
Insurance Status					
Private	97,257 (59.96)	19,579 (42.9)	11,197 (54.5)	64,741 (60.1)	32,516 (59.7)
Public	50,835 (31.3)	14,074 (30.8)	8,731 (42.5)	30,210 (28)	20,625 (37.9)

Education					
Less than HS	10,736 (6.6)	2,344 (5.1)	1,344 (6.5)	7,915 (7.4)	2,821 (5.2)
High School	17,738 (10.94)	2,457 (5.4)	1,871 (9.1)	9,977 (9.3)	7,761 (14.3)
More than HS	30,816 (19)	2,675 (5.9)	1,856 (9)	14,352 (13.3)	16,464 (30.2)
Marital Status					
Married	95,144 (58.7)	27,772 (60.8)	11,530 (56.1)	59,668 (55.4)	35,476 (65.1)

Table 6: Postpartum Hemorrhage Model (n = 51,372; n = 50,335 for random sample)

Variable	Odds Ratio (95% CI)	OR (95% CI) for Random Sample of Women (1 entry per woman)
Oxytocin Cat 6000-15000 mU vs 0-6000 mU	1.74 (1.55-1.96)	1.65 (1.47-1.87)
Oxytocin Cat 15000-27000 mU	2.51 (2.08-3.04)	2.5 (2.07-3.02)
Maternal Conditions		
Chronic Diabetes	0.79 (0.51-1.24)	0.69 (0.43-1.1)
Gestational Diabetes	1.21 (0.98-1.52)	1.2 (0.96-1.5)
Chronic Hypertension	1.2 (0.81-1.8)	1.3 (0.86-1.94)
Gestational Hypertension	1.83 (1.51-2.22)	1.83 (1.5-2.23)
Superimposed Preeclampsia	4.26 (2.92-6.24)	4.2 (2.84-6.21)
Severe Preeclampsia	3.49 (2.62-4.67)	3.69 (2.77-4.91)
Moderate Preeclampsia	3.1 (2.56-3.75)	3.14 (2.59-3.81)
Eclampsia	5.78 (2.22-15.05)	6.19 (2.36-16.2)
Magnesium Sulfate	0.99 (0.95-1.03)	0.99 (0.95-1.03)
Large for Gestational Age Fetus	1.02 (0.99-1.05)	1.02 (0.99-1.05)
Intrapartum Fever	1.93 (1.56-2.39)	1.97 (1.6-2.43)

Table 6 continued

Variable	Odds Ratio (95% CI)	OR (95% CI) for Random Sample
Entry 2 vs Entry 1	0.93 (0.75-1.16)	
Entry 3	0.56 (0.18-1.78)	
Attendant Midwife vs MD	3.54 (2.34-5.33)	3.46 (2.28-5.23)
Attendant Team vs MD	1.05 (0.83-1.33)	1.05 (0.83-1.33)
Teaching Community vs University	0.81 (0.64-1.03)	0.8 (0.62-1.01)
Non-teaching	0.87 (0.68-1.13)	0.88 (0.68-1.13)
Black vs White	1.06 (0.89-1.25)	1.05 (0.89-1.25)
Hispanic	1.73 (1.5-1.99)	1.72 (1.49-1.99)
Asian/PI	1.89 (1.46-2.45)	1.81 (1.38-2.36)
Gestational Age	1.06 (1.03-1.09)	1.06 (1.02-1.09)
Maternal Age	1.01 (1.00-1.02)	1.01 (0.997-1.02)

Table 6 continued

Variable	Odds Ratio (95% CI)	OR (95% CI) for Random Sample
Parity	1.01 (0.97-1.06)	1.01 (0.96-1.05)
BMI		
<= 18.4 vs 18.5-24.9	1.18 (0.91-1.53)	1.15 (0.89=1.49)
25-29.9	0.86 (0.75-0.98)	0.87 (0.76-1.01)
30-34.9	0.96 (0.8-1.16)	0.97 (0.81-1.17)
35-39.9	0.9 (0.7-1.17)	0.91 (0.81-1.17)
>= 40	0.91 (0.78-1.05)	0.9 (0.78-1.05)
Delivery Cesarean vs Vaginal	0.67 (0.56-0.79)	0.67 (0.57-0.79)
Max Infusion <= 20 mU/min vs <= 10 mU/min	1.3 (1.15-1.47)	
Max Infusion > 20 mU/min	2.11 (1.81-2.46)	

Table 7: Primary Cesarean Section Model (n = 51,451; n= 50,413 for random sample model)

Variable	Odds Ratio (95% CI)	OR (95% CI) for Random Sample
Oxytocin Cat 4200 mU	1.26 (1.16-1.36)	1.25 (1.16-1.35)
Oxytocin Cat 7800 mU	1.82 (1.67-1.99)	1.85 (1.69-2.01)
Oxytocin Cat 12000 mU	2.61 (2.39-2.85)	2.63 (2.41-2.86)
Maternal Conditions		
Chronic Diabetes	2.1 (1.74-2.54)	2.11 (1.75-2.56)
Gestational Diabetes	1.24 (1.1-1.41)	1.24 (1.1-1.41)
Chronic Hypertension	1.54 (1.27-1.86)	1.57 (1.29-1.91)
Gestational Hypertension	1.14 (1.02-1.28)	1.16 (1.03-1.3)
Superimposed Preeclampsia	2.45 (1.88-3.21)	2.45 (1.87-3.21)
Severe Preeclampsia	2.76 (2.31-3.3)	2.82 (2.36-3.36)
Moderate Preeclampsia	1.46 (1.28-1.65)	1.47 (1.29-1.66)
Eclampsia	5.03 (2.38-10.64)	5.37 (2.49-11.59)
Magnesium Sulfate	0.94 (0.93-1.2)	0.94 (0.93-0.97)
Large for Gestational Age Fetus	1.09 (1.07-1.1)	1.09 (1.07-1.1)
Intrapartum Fever	1.93 (1.71-2.17)	1.95 (1.74-2.19)

Table 7 continued

Variable	Odds Ratio (95% CI)	OR (95% CI) for Random Sample
Entry 2 vs Entry 1	0.46 (0.37-0.55)	
Entry 3	1.32 (0.56-2.62)	
Teaching vs University	0.39 (0.35-0.44)	0.39 (0.35-0.43)
Non-teaching	0.5 (0.44-0.56)	0.5 (0.45-0.57)
Black vs White	1.62 (1.45-1.72)	1.62 (1.49-1.77)
Hispanic	1.31 (1.19-1.42)	1.32 (1.21-1.44)
Asian/PI	1.3 (1.1-1.48)	1.3 (1.12-1.52)
Gestational Age	1.06 (1.05-1.09)	1.06 (1.04-1.08)
Maternal Age	1.05 (1.04-1.05)	1.05 (1.05-1.06)
Parity	0.43 (0.42-0.46)	0.42 (0.4-0.43)

Table 7 continued

Variable	Odds Ratio (95% CI)	OR (95% CI) for Random Sample
BMI		
<= 18.4 vs 18.5-24.9	0.83 (0.7-0.99)	0.83 (0.7-0.99)
25-29.9	1.32 (1.22-1.43)	1.33 (1.23-1.44)
30-34.9	1.6 (1.45-1.77)	1.62 (1.46-1.79)
35-39.9	1.98 (1.74-2.26)	2.03 (1.78-2.31)
>= 40	1.25 (1.16-1.36)	1.26 (1.16-1.36)
Max Infusion > 10 to <= 20 mU/min vs <= 10 mU/min	1.07 (0.99-1.14)	
Max Infusion >20 to <= 40 mU/min	2.23 (2.06-2.42)	
Max Infusion > 40 mU/min	2.83 (1.87-4.3)	

Table 8: Postpartum Hemorrhage Model, stratified by Site

Oxytocin Total Dose Categories (mU)	Site 41* OR (95% CI) n = 28,143	Site 42 OR (CI) n = 3,267	Site 44 OR (CI) n = 11,771	Site 46 OR (CI) n = 3,182	Site 52 OR (CI) n = 3,695
6000	1.57 (1.33-1.85)	2.15 (1.44-3.2)	1.62 (1.28-2.05)	1.85 (.185-2.89)	Empty**
15000	2.59 (1.92-3.49)	1.96 (1.09-3.51)	2 (1.89-3.52)	2.29 (1.07-4.88)	Empty**

* Site 41 was missing any data on antenatal large for gestational age, so this variable was dropped from the model. In addition, only 6 women from the site were marked as having eclampsia. This variable was also removed from the model.

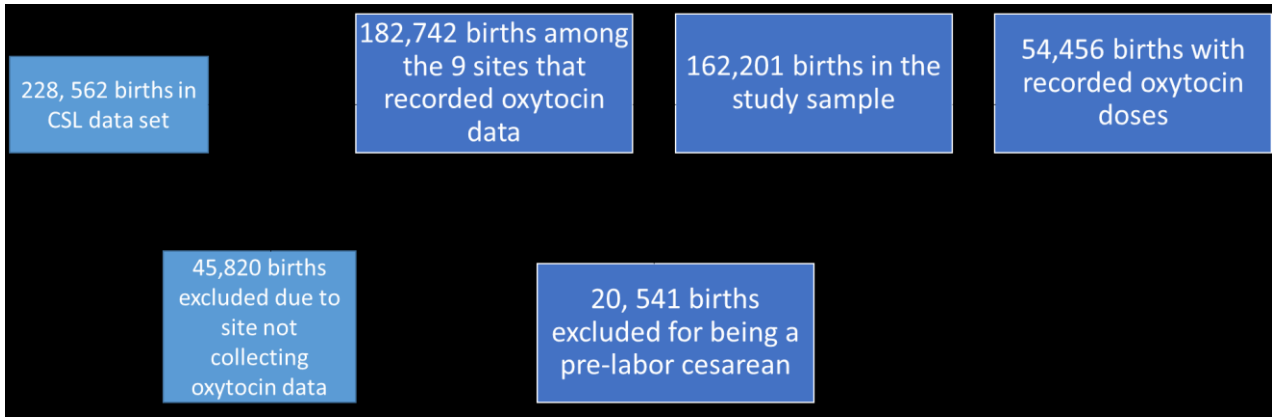
** Both of these categories were empty due to collinearity.

Table 9: Primary Cesarean Section Model, stratified by Site

Oxytocin Total Dose Categories (mU)	Site 41 OR (95% CI) n = 28,143	Site 42 OR (CI) n = 3,316	Site 44 OR (CI) n = 11,793	Site 46 OR (CI) n = 3,349	Site 52 OR (CI) n = 3,795
4200	1.17 (1.05-1.3)	0.97 (0.7-1.34)	1.44 (1.26-1.65)	1.2 (0.93-1.56)	Empty*
7800	1.8 (1.6-2.04)	1.51 (1.08-2.13)	2 (1.73-2.32)	1.46 (1.07-1.99)	2 (0.14-28.07)
12000	2.72 (2.38-3.11)	2.22 (1.67-2.95)	2.88 (2.51-3.3)	1.62 (1.18-2.24)	3.38 (0.51-22.63)

*Model dropped the three observations in this category.

Figure 4: Sample Flow Diagram



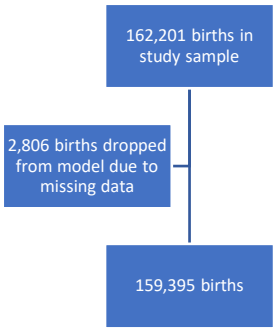


Figure 5: Oxytocin Prevalence Model Sample

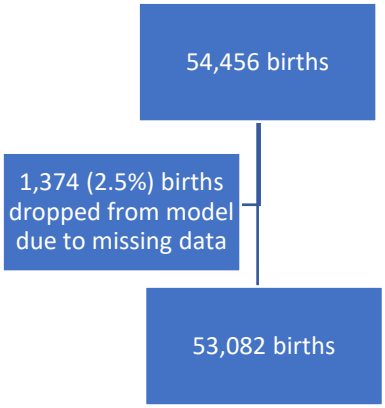


Figure 6: Postpartum Hemorrhage Model Sample

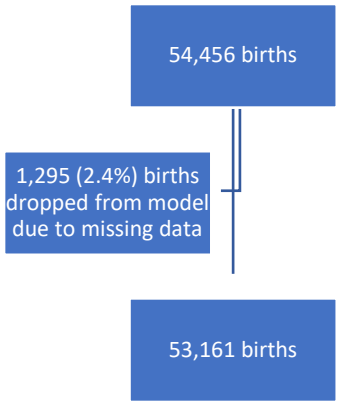


Figure 7: Primary Cesarean Model Sample

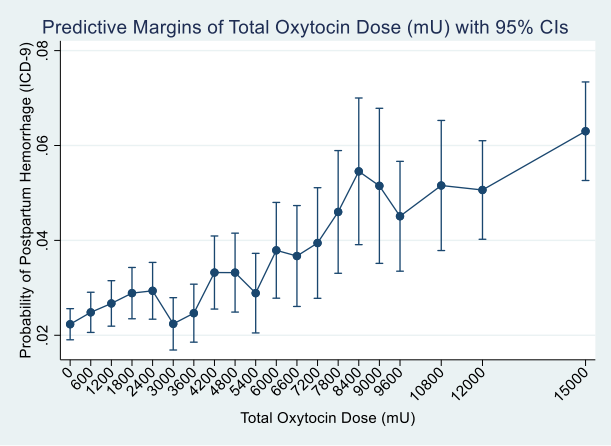
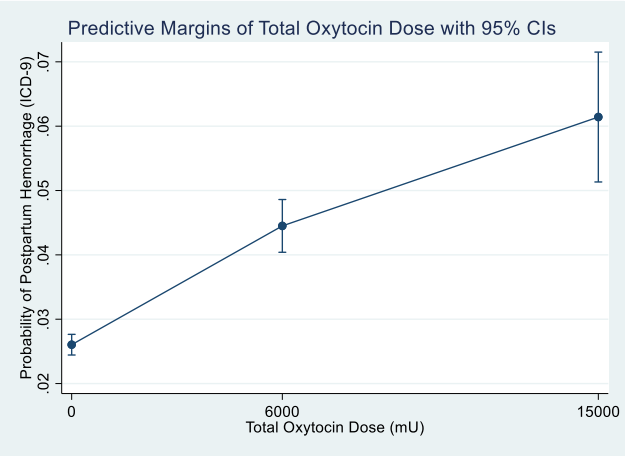


Figure 8: Probability of PPH based on Oxytocin Total Dose (mU)

Figure 9: Probability of PPH based on Oxytocin Total Dose (mU), below



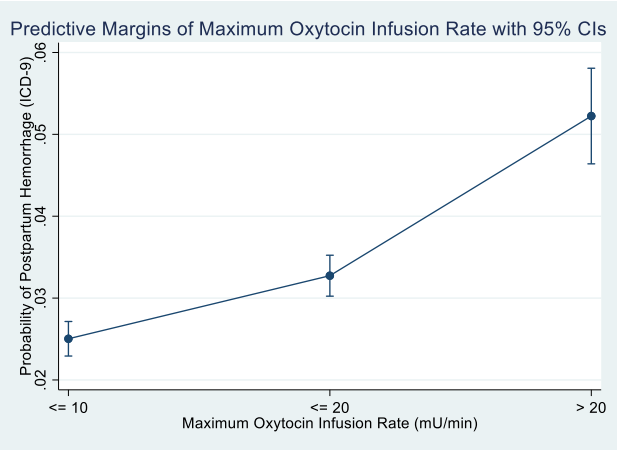


Figure 10: Probability of PPH by Maximum Infusion Rate (mU/min)

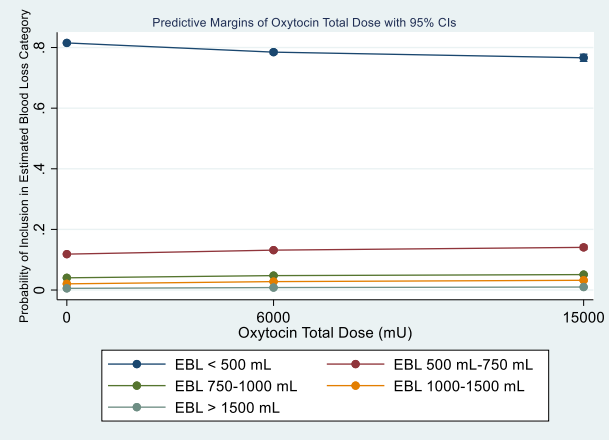


Figure 11: Probability of Estimated Blood Loss (mL) by Oxytocin Total Dose (mU)

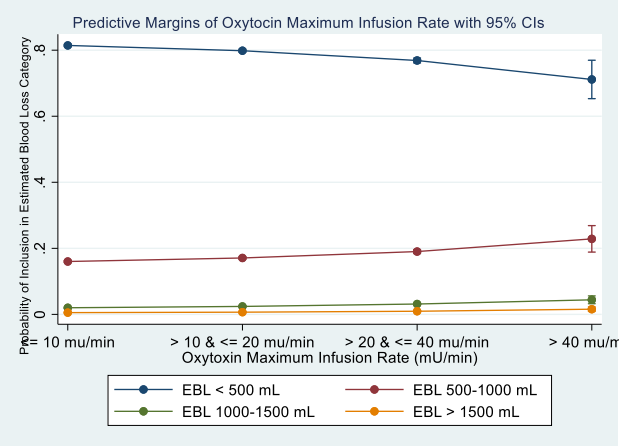


Figure 12: Probability of Estimated Blood Loss (mL) by Oxytocin Maximum Infusion Rate (mU/min)

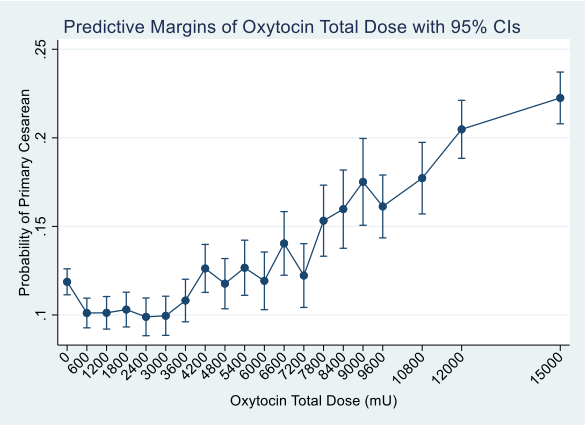


Figure 13: Probability of Primary Cesarean Section based on Oxytocin Total Dose (mU)

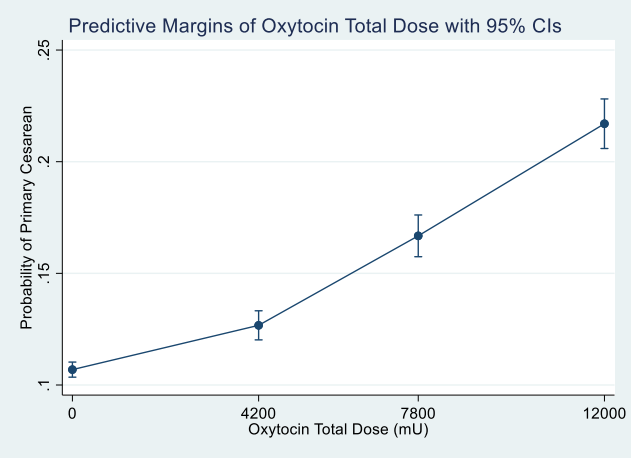


Figure 14: Probability of Primary Cesarean Section by Oxytocin Total Dose (mU)

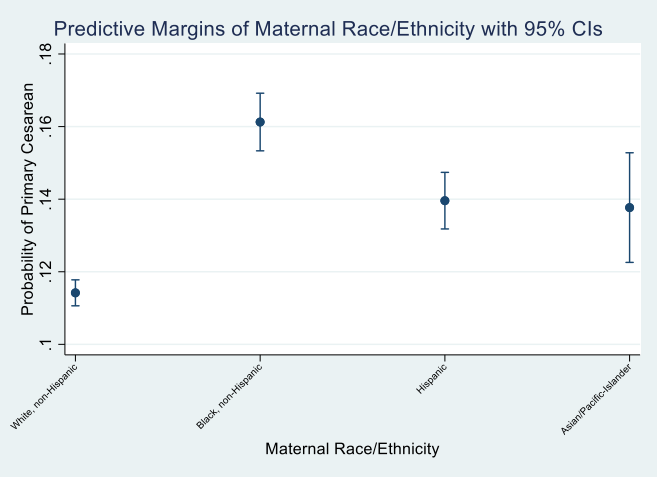


Figure 15: Probability of Primary Cesarean by Maternal Race/Ethnicity

oxy_cat	Freq.	Percent	Cum.
0	10,931	20.28	20.28
600	5,859	10.87	31.14
1200	4,887	9.06	40.21
1800	4,179	7.75	47.96
2400	3,445	6.39	54.35
3000	3,089	5.73	60.08
3600	2,693	5.00	65.07
4200	2,291	4.25	69.32
4800	1,944	3.61	72.93
5400	1,703	3.16	76.09
6000	1,470	2.73	78.81
6600	1,280	2.37	81.19
7200	1,147	2.13	83.32
7800	1,065	1.98	85.29
8400	882	1.64	86.93
9000	744	1.38	88.31
9600	1,296	2.40	90.71
10800	1,029	1.91	92.62
12000	1,760	3.26	95.88
15000	2,219	4.12	100.00
Total	53,913	100.00	

Table 9: Oxytocin total dose categories

Key
frequency *row percentage* *column percentage*

	momrace_new						
oxy_dose_cat	white/non	black/non	Hispanic	Asian/Pac	Mutl-raci	other	Total
<= 10 mu/min	14,709	4,458	3,232	681	32	119	23,231
	63.32	19.19	13.91	2.93	0.14	0.51	100.00
	43.96	44.92	42.73	45.34	68.09	55.09	44.07
> 10 & <= 20 mu/min	15,724	2,890	2,898	564	12	73	22,161
	70.95	13.04	13.08	2.55	0.05	0.33	100.00
	46.99	29.12	38.32	37.55	25.53	33.80	42.04
> 20 & <= 40 mu/min	2,974	2,543	1,411	251	3	24	7,206
	41.27	35.29	19.58	3.48	0.04	0.33	100.00
	8.89	25.62	18.66	16.71	6.38	11.11	13.67
> 40 mu/min	52	33	22	6	0	0	113
	46.02	29.20	19.47	5.31	0.00	0.00	100.00
	0.16	0.33	0.29	0.40	0.00	0.00	0.21
Total	33,459	9,924	7,563	1,502	47	216	52,711
	63.48	18.83	14.35	2.85	0.09	0.41	100.00
	100.00	100.00	100.00	100.00	100.00	100.00	100.00

Table 10: Maximum Oxytocin Infusion Rate by Maternal Race/Ethnicity

CONCLUSION

Oxytocin is a high-alert medication because it is the obstetric drug most commonly associated with preventable adverse outcomes.[1,57(p32)] Oxytocin is a key ingredient in half of all paid obstetric litigation claims.[57(p33),108] It is also a life-saving medication. So, what are appropriate rates of oxytocin use? In low-to-moderate risk women, the need for oxytocin use may be as low as 4.5 to 8.8%.[80(p21),120(p17)] The World Health Organization reports augmentation is needed in less than 30% of labors[110(pS270)]. In contrast, *most* women in the US and in other high-resource countries are exposed to oxytocin during labor. Studies from several European countries concluded that oxytocin is frequently used without an indication. Preventive[57,97,111,112] or interventive[113–115] measures to decrease excessive use or misuse of oxytocin exist, but it is unclear to what extent they have been adopted.

A persistent difficulty in the study of oxytocin is measurement. Many studies use "induction" or "augmentation" as variables, but both induction and augmentation are simply markers for an array of medications and procedures. The measures are heterogenous and the research findings are heterogenous due to a lack of specificity in measurement. While oxytocin would be best captured as a continuous variable, most studies use a binary variable (i.e., exposed to oxytocin – yes or no). In all of these studies, oxytocin exposure is measured as a binary variable[33,35,72–76]; further quantification of oxytocin exposure in the US among laboring women is not readily available. The use of a binary variable "loses" most of the information about a continuous variable. Recent studies have pioneered different measures, predominantly categorical, to better understand oxytocin use. There has been little methodological conversation, however, around the rationale behind these measures and which measure is best pharmacologically, physiologically and clinically. Several studies have used "total dose" to

measure oxytocin but ended up creating categories because the continuous variable was difficult to interpret clinically. One difficulty in these studies is a lack of consistent measurements (e.g., comparing percentiles[50] of oxytocin dose to 5000 mU increases[14]). To add to the confusion, some studies have referred to "area under the curve" and others "total dose" to refer to the same measure. Researchers might consider using additional measures of oxytocin exposure that provide more information and greater clinical utility than a binary variable. Some examples include: total dose (mU); maximum infusion rate (mU/min); and total duration (min). Further research is needed to determine the best categorical measures of oxytocin exposure.

Initially, oxytocin exposure was going to be examined as a continuous variable (total dose, mU). Using this variable was difficult to interpret, however, so the decision was made to create two different categorical variables that would be easier to interpret clinically. The first variable created categories by 600 mU (the total dose of oxytocin in mU after an hour of receiving a 10 mU/min infusion) up to 9600 mU, followed by a category at 10800, 12000 and 15000 mU. 10,800 mU was close to the 90th percentile for oxytocin exposure in the data set (10,914 mU) and equivalent to an additional hour of oxytocin exposure at 20 mU/min; 12,000 mU was equivalent to an additional hour of exposure to a 20 mU/min oxytocin rate. 15000 mU was close to the 95th percentile (15,114 mU). In the dataset, the 25th percentile was 860 mU and the 50th percentile was 2,618 mU. The rationale in creating these categories was to have small increases that were clinically understandable. The second variable was infusion rate categories at $\leq$ 10 mU/min, $\leq$ 20 mU/min, $\leq$ 40 mU/min and $\geq$ 40 mU/min. Again, these categories were created based on clinical relevance as most oxytocin policies have a maximum dose of 20 mU/min or, less frequently, 40 mU/min.

Studies looking to examine induction or augmentation should parse the medications or practices being used so that the outcomes of the studies are easier to understand. Induction is "easy" to look at because it has an ICD-10 code, but the heterogeneity of induction practices and protocol makes it an unhelpful study variable. It is more difficult to examine augmentation as there is currently no associated ICD-10 code. Further, augmentation involves an array of practices and protocols which means that this, too, is not necessarily a helpful study variable. Future studies might delineate the specific procedure or medication being used to augment labor, the procedure or medication protocol and whether woman is being augmented before or after she is in active labor (>= 6 cm cervical dilation).

"Spontaneous labor" is frequently used as sample inclusion criteria in augmentation studies; but spontaneous labor does not necessarily mean active labor, which is perhaps the more relevant marker. Recent studies have demonstrated that labor should be called active when cervical dilation is greater than or equal to six centimeters. To improve clinical practice, better understand adverse effects related to oxytocin and enable comparison between studies, the new definition of active labor should be used consistently.

While there is some inconsistency in the findings of these studies – due, in part, to the nature of the research questions and binary measurement of oxytocin – the overarching finding is that oxytocin exposure is an independent risk factor for postpartum hemorrhage. There is evidence that even two hours on a 20 mU/min infusion of oxytocin substantially increases the risk of severe postpartum hemorrhage, as does increasing the infusion rate above 20 mU/min. Further research is needed, however, to corroborate these findings, refine the understanding of oxytocin's association with hemorrhage (e.g., are there clinically relevant points in oxytocin exposure where risk for hemorrhage increases exponentially? Are there points that are suggested

by the data, clinical practice or physiology?) and to translate these findings to inform clinical practice. One immediate suggestion, however, would be to include the potential increased risk for postpartum hemorrhage in providing informed consent to women around oxytocin use in labor.

To better understand the relationship between oxytocin exposure in labor and the risk of cesarean section, more detailed information about oxytocin is needed. Such variation exists in each woman's exposure to oxytocin, that observing oxytocin exposure as a binary variable may, in fact, obscure more than it elucidates.

While frequent use of oxytocin in the intrapartum is documented in a variety of high-income countries, none of them have rates of maternal and neonatal morbidity and mortality as high as the United States. This suggests that while over- and inappropriate use of oxytocin may contribute in part to morbidity and poor-quality outcomes, it is not the entire story. More research is needed regarding decision-making and communication around oxytocin use in the intrapartum. The research should be woman-centered and include outcomes that are important to women.[43] Well-delineated definitions and measures are essential and may also require further research to develop.

Practice changes are needed to shift obstetric culture and how we use oxytocin. Two related foci for change are using the minimal amount of oxytocin necessary and addressing misuse of oxytocin (e.g., augmentation without an indication). Checklists, partograms and turning oxytocin off in active labor hold promise as ways to address both misuse and overuse.[41,57,97,111–115] Other potential interventions include one-on-one support, either with nurses or doulas.[117,118]

Nurses have a critical role in practice change, as they are the care provider at the bedside, assessing the patient and, frequently, the one alerting the attending physician or midwife as to whether or not intervention is needed. Nurses advocate for their patients and are capable of tracking the total dose of oxytocin a woman has received or questioning a provider's oxytocin order if it seems inappropriate or unsafe. Midwives are known for supporting physiologic birth and preventing unnecessary intervention, but the practice culture in which they work make affect their clinical decision-making.[154] Nurses and midwives are both able to advocate for practice change, to question whether starting oxytocin is appropriate, to use partograms and a more conservative (i.e. 6 cm dilation) definition of active labor in determining whether intervention is appropriate. Finally, nurses and midwives are uniquely suited to educating women, providing them with information so that women can make a truly informed choice regarding intervention during their labors.

Oxytocin, the life-saving high-alert medication, is overused in US obstetric practice. If practice in other high-income countries is similar to US practice, it is mis-used as well, especially in the context of labor augmentation. Specific oxytocin total doses and infusion rates are associated with a greater risk of postpartum hemorrhage and primary cesarean section. The way oxytocin is currently used in US obstetrics is tied to many factors, patient, provider and hospital. It will take a culture-change in obstetrical care to shift how we use oxytocin, but such change is possible. Oxytocin use is tied to maternal morbidity and quality outcomes, but its use, while frequent in other high-resource countries, is not associated with the same degree of adverse maternal and neonatal outcomes as we see here in the US. Oxytocin is just a piece in a much larger jigsaw puzzle, but a critical piece and one amenable to intervention to improve outcomes. The call for more judicious oxytocin use is not new[41], but it is time to act.

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Presentations

Rao, K., Warren, N., Mayra, K., Srivastava, S., Safley, R., and Gupta, J. "AMANAT Evaluation" (poster), International Confederation of Midwives 2017 Triennial Conference, Toronto, Canada

Safley, R. and Swietlikowski, J. "PAIN MANAGEMENT IN OPIOID-DEPENDENT PREGNANT WOMEN" (podium), American College of Nurse-Midwives (ACNM) 2017 Annual Conference, Chicago, IL

Safley, R. "ADAPTING THE QUALITY-CARING MODEL TO GUIDE WOMEN-CENTERED CARE IN THE THIRD STAGE OF LABOR" (podium), International Council on Women's Health Issues 2016 Annual Conference, Baltimore, MD

Safley, R. "THOSE MAGIC MOMENTS: The state-of-the-science regarding the Third Stage of Labor" (podium), ACNM 2016 Annual Conference, Albuquerque, NM

LeGros, C. and Safley, R. "HACKS FOR THE FIRST FIVE YEARS: Advice and Encouragement for Young Midwives" (podium), ACNM Annual Conference, July 2015, Washington, DC

Research Experience

JOHNS HOPKINS UNIVERSITY, December 2015 – Present

- **Secondary data analysis of the Consortium on Safe Labor Database**
- **Worked on data management and analysis with intimate partner violence data**
- **Assisted primary mentor with tool development for measuring obstetric nursing quality in India**

Teaching Experience

JOHNS HOPKINS UNIVERSITY, May 2016 – Present

- **Teaching Assistant for Obstetric Nursing course, Fall 2016-December 2017**
  - **Maintain the Discussion Board on Blackboard, held office hours, facilitated exam preparation and review sessions, participated in course review and planning, developed abilities to respond to and incorporate student and faculty feedback, participated in exam improvement efforts with faculty**
  - **Guest lectured on Postpartum Hemorrhage**
- **Teaching Assistant for Biostatistics, Summer 2016**
  - **Responsible for office hours, running exam review sessions with students, reporting and responding to student feedback**
  - **Guest lectured for two class sessions**
- **Completed nurse educator certificate courses as doctoral electives**
- **Participates in Center of Integration for Research, Teaching and Learning courses for teaching enrichment, Fall 2016 – Present**

ADVANCED LIFE SUPPORT in OBSTETRICS, April 2013 - Present

- **Certified Instructor**

SHENANDOAH UNIVERSITY, January 2013 – July 2015

- **Preceptor for midwifery students**

WEST VIRGINIA UNIVERSITY, Fall 2012 – July 2015

- **Preceptor for medical students**

SHEPHERD UNIVERSITY, Shepherdstown, WV, September 2011 – December 2012

- **Clinical instructor for students in the bachelors of nursing program**

Professional Engagement

JOURNAL OF MIDWIFERY AND WOMEN'S HEALTH, June 2016-Present

- **Peer reviewer for the journal**
- **Award Selection Committee, 2017**

STUDENT AND NEW MIDWIVES COMMITTEE, American College of Nurse-Midwives, January 2015-Present

- **Provide support and feedback for students and new midwives, assist students in drafting their recommendations to the ACNM Board and work with committee members to develop resources for students and new midwives.**

Professional Experience

SHENANDOAH VALLEY COMMUNITY HEALTH, Martinsburg, WV, June 2011 – July 2015

- **Certified Nurse-Midwife providing gynecological, antepartum, intrapartum and postpartum care to high-, medium- and low-risk women on Medicaid or uninsured with significant numbers of teenagers, undocumented workers and substance users**
- **Admitting privileges at Berkeley Medical Center (West Virginia University-affiliate hospital) for health center patients and drop-ins, surgical first assist for caesarean sections**
- **Participant in the National Health Service Corps, June 2012 – June 2015**

HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA, Philadelphia, PA, January 2008 – May 2010

- **Staff Registered Nurse on a Medical-Surgical Floor in a tertiary care referral center, unit specializes in pulmonary, gastroenterology, renal, infectious disease and internal medicine, experienced in acute and long-term care**
- **Recipient of the DAISY Award for Extraordinary Nurses, February 2009**

Certifications and Licenses

Certified Nurse Midwife, January 2011 - Present

- **DEA and NPI available on request**

Women's Health Nurse Practitioner – Board-Certified, January 2011 – Present

Registered Nurse, January 2008 - Present

- **License in PA pending; License in MD inactive**

Advanced Life Support in Obstetrics Instructor, June 2013 - Present

Neonatal Resuscitation Provider, 2010 - Present

Basic Life Support Provider, 2006 - Present

Precision Nutrition Level 1 Coach, In Progress

Restorative Exercise Specialist, In Progress

Professional Organizations

AMERICAN COLLEGE OF NURSE-MIDWIVES, 2010 – Present

AMERICAN NURSES ASSOCIATION, 2015 – Present

SIGMA THETA TAU, 2007 – Present

PHI BETA KAPPA, 2005 – Present

Community Engagement_____

Program Advisor, Master in Pastoral Care and Counseling Program, Antiochian House of Studies, UNIVERSITY OF BALAMAND, 2016 – Present

- **Provide health care expertise, research advice for students' thesis work, curriculum feedback and participate in the students' annual residency**